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Sustained Drug Release from Tablets and Particles Through Coating

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I. INTRODUCTION

Probably the earliest work in the area of sustained drug delivery dosage forms can be traced to the 1938 patent of Israel Lipowski [1]. This work involved coated pellets for prolonged release of a drug, and was presumably the forerunner to the development of the coated-particle approach to sustained drug delivery that was introduced in the early 1950s. There has been 40 years of research and development experience in the sustained drug release area since that patent, and a number of strategies have been developed to prolong drug levels in the body. These range from the very simple slowly dissolving pellets or tablets to the more technologically sophisticated controlled drug-release systems which have recently started to appear on the market and in the pharmaceutical literature [2–13]. The endpoint in all of these systems is the same in that extended durations of drug levels are sought, but the method of achieving this endpoint and the clinical performance of these products can vary considerably. Successful fabrication of sustained-release products is usually difficult and involves consideration of the physical–chemical properties of the drug, pharmacokinetic behavior of the drug, route of administration, disease state to be treated and, most importantly, placement of the drug in a dosage form that will provide the desired temporal and spatial delivery pattern for the drug. This chapter is devoted to an examination of one method of sustained-release drug delivery; namely, coating.

The approach in this chapter is to present the requirements for a sustained-release product in terms of the appropriate release rate of drug from the dosage form, a brief review of those factors influencing the design and performance of a sustained-release product, such as the physical–

Table 1 Some Therapeutic Advantages of Sustained-Release Systems

1. Avoid patient compliance problems	
2. Employ less total drug	Minimize or eliminate local side effects
	Minimize or eliminate systemic side effects
	Less potentiation or reduction in drug activity with chronic use
	Minimize drug accumulation with chronic dosing
3. Improved efficiency in treatment	Cure or control of condition more promptly
	Improved control of condition; i.e., less fluctuations in drug level
	Special effects, e.g., sustained-release aspirin provides sufficient drug so that on awakening the arthritic patient has symptomatic relief

Source: From Ref. 21.

chemical properties of the drug and the type of delivery system employed, and lastly, a reasonably critical review of coating as an approach to sustained-drug delivery. Numerous chapters and articles have been written about the technology of specialized coatings, the theoretical foundation for these products, and the resulting clinical and pharmacokinetic assessment. We have no intention of duplicating this effort and, for the sake of brevity, our approach will be to touch on each of these areas without attempting to be comprehensive. Thus, this chapter should serve as a starting point for the pharmaceutical scientist wishing to prepare a coated sustained-release product.

At the outset it may seem unnecessary to justify sustained-release products, but there are some who still view these products as convenience items that offer little clinical benefit to the patient. Indeed the therapeutic advantages of sustained-release products over their nonsustained counterparts are well documented in the literature. Some of these advantages are shown in Table 1. Aside from the enormous advantage of overcoming patient compliance problems, well-designed sustained-release dosage forms offer considerable potential in terms of the temporal and spatial delivery of drug and the resulting maintenance of drug levels in tissues of the body. This suggests that all drugs ought to be placed in a sustained-release form, but this is often not feasible and/or practical.

There are many different definitions of sustained release, but we will adopt the brief, simple definition of sustain d-release drug systems as *any*

drug or dosage form modification that prolongs the therapeutic activity of the drug. Further, in the absence of suitable clinical evidence of this sustaining effect, we shall accept prolongation of drug levels in the blood. Accordingly, a prodrug or analog modification of the drug that sustains drug activity, or blood drug levels, is viewed as a sustained-release system in the same sense as an alteration in the dosage form.

There are literally dozens of names associated with sustained-release products, such as timed release, prolonged release, controlled release, etc., and this has led to a great deal of confusion. We shall adopt the term *sustained release* to indicate a prolonged release of drug from the dosage form, irrespective of the mechanism or duration of this sustaining effect. Thus, a repeat-action dosage form will be referred to as a sustained-release product, as will the more common prolonged-release type. Moreover, we will use the terms prolonged release and sustained release interchangeably.

Sustained-release products have received a substantial amount of attention in recent years, and several good reviews are available for the interested reader [3–7,14–20]. These reviews provide not only a description of the available mechanisms and technology for production of these dosage forms, but also information on clinical evaluation and performance. Information on coating technology for sustained-release products, although extensive in the pharmaceutical industry is, unfortunately, rather sparse in available published form. Fields outside of pharmacy making use of sustained-release principles do contain a relatively rich supply of information, specially about polymer properties [22–25], that can sometimes be used for pharmaceutical application. However, this information usually cannot be directly translated into pharmaceutical practice because of the uniqueness of the pharmaceutical dosage form.

II. REQUIREMENTS FOR SUSTAINED DRUG RELEASE

Design of a sustained-release product is normally a very difficult task because of the interplay of the physical–chemical–biological properties of the drug, the patient-disease state, and technological limitations in fabrication of the final dosage form. Depending on the drug, disease state, route of administration, and the like, some of these points will be less important than others, but before a final decision is made to proceed with the dosage form, all of these factors must be considered. To give some perspective on the deliberations that are required as well as establish some guidelines for design of sustained-release products it is worthwhile to briefly review those factors playing a substantial role in the design of sustained-release products.

A. Release Rate and Dose Concentrations

An ideal type of sustained-release product would be one in which the rate of drug delivery is phased to the needs of the condition at hand. Thus, such factors as moment-to-moment variations in drug needs of the condition could be incorporated into the drug-release pattern [26,27]. However, we generally lack the technological sophistication to prepare a

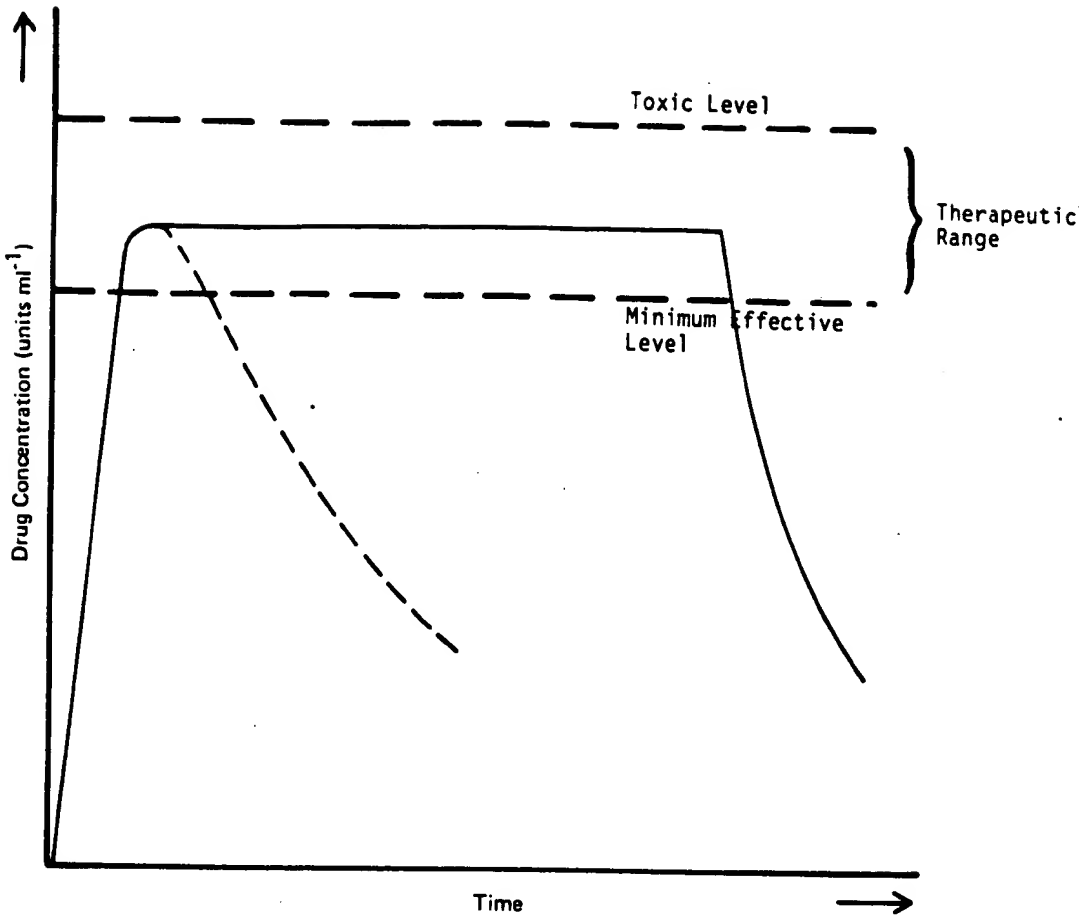
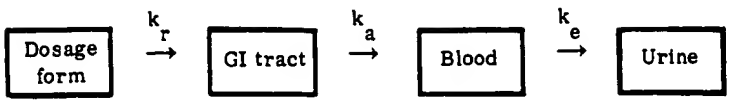


Figure 1 "Ideal" sustained blood or tissue drug level versus time profile. The corresponding level from a nonsustained unit is shown as the dashed line.

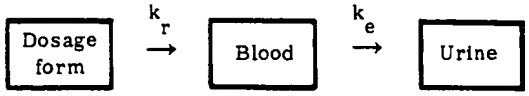
product with such a variable release rate, and indeed we frequently do not understand the drug needs of the condition sufficiently to incorporate this into the design of the product. In fact, we can think of only one sustained-release system that meets the criteria of an ideal product, and that is the so-called artificial pancreas. In this system, an implantable electrode monitors the level of circulating glucose and releases an amount of insulin based on the needs of the condition [28].

What is more commonly done with a sustained-release product is to generate a tissue or blood drug concentration versus time profile whereby the level of drug is maintained constant throughout therapy, as is depicted in Figure 1. In this approach, it is assumed that the biological activity of drug instantaneously mirrors blood or tissue drug levels. This is a reasonable assumption that is borne out with many drugs.

For the sake of discussion, the model for oral drugs shown in Schem 1 will be used to describe drug movement in the body, wher k_r, k_a, and k_{el} represent the rate constants for drug release, absorption, and elimination, respectively. For a sustained-releas dosag form k_r is much



Scheme 1



Scheme 2

smaller than k_a, thus becoming rate limiting in the above catenary scheme and reducing the model to that shown in Scheme 2.

If indeed we wish to maintain a constant level of drug in some desired target tissue, the next logical question is what release pattern from the dosage form (drug input) is needed to produce such a profile. It can easily be shown that a zero-order release of drug from the dosage form or, conversely, availability to the body is the most appropriate release pattern [3,29]. The following discussion is pertinent to the question of the desired release rate. For a drug whose disposition in the body can be described by a simple, one-compartment open model, the rate of drug loss at any point in time can be described as

$$\text{rate out} = k_r^0 = C_t k_{el} V_d \tag{1}$$

where C_t is the concentration of drug in the blood (or tissue) at a particular point in time, k_{el} is the total elimination rate constant, and V_d is incorporated into the equation to convert from concentration to an amount basis and is the apparent volume of distribution for the drug. For illustration purposes refer to Figure 1; the desired concentration of a drug is shown as the plateau concentration or maximum in the nonsustained blood drug level profile, which presumably would be the midpoint of the therapeutic range. If we wish to maintain this drug level indefinitely, it is only necessary to put the drug back in at the same rate it is being removed, or

$$\text{rate in} = \text{rate out} = k_r^0 = C_t k_{el} V_d \tag{2}$$

Note that the units resulting from equation 2 are weight (dose) per unit time or that to maintain a constant level of drug it is necessary to provide drug at a constant rate to replace that which is lost. One can envision the simplest sustained drug product as an intravenous drip whereby the rate of drug supply matches that which is lost and is constant (zero-order). For oral and other routes of drug administration, we ther for wish to provide drug via a zero-order pattern whose rate constant describing delivery is determined by the terms shown in equations 1 and 2. For

drugs showing more complex disposition patterns than a simple one-compartment model, suitable mathematics can be generated to produce the appropriate rate constant for release of drug from a sustained-release unit [26,27].

To determine the total amount of drug for the dosage form one merely adds the amount of drug needed to achieve the desired blood level quickly (the immediately available portion) to the sustaining portion. The sustaining portion is determined by multiplying the zero-order rate constant for sustained drug delivery, k_r^0, by the desired sustaining time, h [29]:

$$W = D_i + k_r^0 h \tag{3}$$

where W is the total dose and D_i is the initial dose. If drug is released via a first-order process, the appropriate equation [29] is

$$W = D_i + \frac{k_{el} C_t V_d}{k_r^1} \tag{4}$$

where k_{el} is the total elimination constant for the drug, C_t is the desired blood concentration, V_d is the volume of distribution for the drug, and k_r^1 is the first-order drug-release rate constant. The last term in equation 4 results from the approximation $D_m = k_{el} C_t V_d / k_r^1$, where D_m is the maintenance dose [29]. For those drug-delivery systems where drug from the sustaining dose is provided to that from the immediate dose at early times, that is, both release drug from time zero, an appropriate correction to the immediately available dose needs to be made [29].

The following example of how the previously described equations can be used will help clarify the discussion.

Sample Calculation for a Sustained-Release Tablet

From a single 500-mg nonsaturated dose of a tablet, the following pharmacokinetic parameters were determined from the blood drug concentration versus time profile:

k_a (absorption) = 2.0 h^{-1}

k_{el} (elimination) = 0.2 h^{-1}

C_t = desired blood level = 10 μg ml^{-1}

V_d = volume of distribution = 42 L

D_i = initial dose = 500 mg or 5,000,000 μg

It is desired to formulate this drug into a sustained-release product releasing drug over a 12-h period such that the serum level is maintained at 10 μg ml^{-1}. Step 1: Using equation 2 from the text

$$\text{Rate in} = \text{rate out} = k_r^0 = C_t k_{el} V_d$$

$$= 10 \text{ μg ml}^{-1} \times 0.2 \text{ h}^{-1} \times 42{,}000 \text{ ml}$$

$$= 84{,}000 \text{ μg h}^{-1}$$

Step 2: After calculating the zero-order release rate constant, k_r^0, calculate the total dose per tablet. Using equation 3 from the text

$$W = D_i + k_r^0 h$$

$$= 500{,}000\ \mu g + (84{,}000\ g\ h^{-1} \times 12\ h)$$

$$= 1{,}508{,}000\ \mu g$$

$$= 1.5\ g \text{ per tablet}$$

Since a large tablet will be generated, the formulator may wish to prepare 0.75-gm tablets so that the patient takes two tablets every 12 h. Conversely, it is possible to reduce the size of the tablet by recalculating for a shorter sustaining time. For example, suppose 6 rather than 12 h of sustaining time is used.

$$W = 500{,}000\ \mu g + (84{,}000\ g\ h^{-1} \times 6\ h)$$

$$= 1{,}004{,}000\ \mu g$$

$$= 1.0\ gm \text{ per tablet}$$

Suppose the formulator finds that the particular sustaining mechanism is better approximated by first-order rather than zero-order release. From the earlier calculations, the formulator knows that for 12 h of release the tablet should contain about 1.5 gm and the zero-order release rate is 84,000 $\mu g\ h^{-1}$. From these data it is possible to approximate the first-order rate constant k_r using equation 4

$$W = D_i + \frac{k_{el} C_t V_d}{k_r^1}$$

$$k_r^1 = \frac{k_{el} C_t V_d}{W - D_i}$$

$$= \frac{0.2\ h^{-1} \times 10\ \mu g\ ml^{-1} \times 42{,}000\ ml}{1{,}508{,}000 - 500{,}000\ \mu g}$$

$$= 8.33 \times 10^{-2}\ h^{-1}$$

B. Drug Properties Considerations

There are a number of physical–chemical and derived biological properties of the drug that either preclude placement of the drug in a sustained-release system or have an adverse influence on product design and performance. Some of these considerations are listed in Table 2. With alm st all of these properties we refer to them as restrictive factors, making formulation of a sustained-release system difficult, but not impossible. Thus, by changing the type of sustaining mechanism, th dose, or th

Table 2 Drug Properties Adversely Influencing a Sustained-Release Dosage Form

Property		Explanation
Physical–chemical properties	Dose size	If an oral product has a dose size greater than 0.5 gm, it is a poor candidate for a sustained-release system, since addition of the sustaining dose and possibly the sustaining mechanism will, in most cases, generate a substantial volume product that will be unacceptably large.
	Aqueous solubility	Extremes in aqueous solubility are undesirable in the preparation of a sustained-release product. For drugs with low water solubility, they will be difficult to incorporate into a sustained-release mechanism. The lower limit on solubility for such product has been reported [30] to me 0.1 mg/ml. Drugs with great water solubility are equally difficult to incorporate into a sustained-release system [31]. pH-Dependent solubility, particularly in the physiological pH range, would be another problem because of the variation in pH throughout the GI tract and hence variation in dissolution rate [31].
	Partition coefficient	Drugs that are very lipid soluble or very water soluble, i.e., extremes in partition coefficient, will demonstrate either low flux into the tissues or rapid flux followed by accumulation in the tissues. Both cases are undesirable for a sustained-release system [32,33].
	Drug stability	Since most oral sustained-release systems, by necessity, are designed to release their contents over much of the length of the GI tract, drugs which are unstable in the environment of

		the intestine might be difficult to formulate into prolonged release systems [34]. Interestingly, placement of a labile drug in a sustained-release dosage form often improves the bioavailability picture [31].
Biological properties	Absorption	Drugs that are slowly absorbed or absorbed with a variable absorption rate are poor candidates for a sustained-release system. For oral dosage forms, the lower limit on the absorption rate constant is in the range of 0.25 h^{-1} [31] (assuming a GI transit time of 10–12 h)
	Distribution	Drugs with high apparent volumes of distribution, which in turn influences the rate of elimination for the drug, are poor candidates [31].
	Metabolism	Sustained-release systems for drugs which are extensively metabolized is possible as long as the rate of metabolism is not too great nor the metabolism variable with GI transit or other routes.
	Duration of action	The biological half-life and hence the duration of action of a drug obviously plays a major role in considering a drug for sustained-release systems. Drugs with short half-lives and high doses impose a constraint because of the dose size needed and those with long half-lives are inherently sustained [16,35].
	Therapeutic	Drugs with a narrow therapeutic range require precise control over the blood levels of drug, placing a constraint on sustained-release dosage forms.

route of administration, it might be possible to generate a sustained-release system. Frequently, a seeminly undesirable property of a drug or dosage form can be overcome or minimized by placement of the drug in a sustained-release system. For example, low drug bioavailability due to instability may sometimes be overcome by placement in a sustained-release system [31].

III. FABRICATION OF SUSTAINED-RELEASE PRODUCTS

Having established the desirable concentration versus time profile as depicted in Figure 1, we can now ask two related questions: What approaches can be taken to achieve this type of profile, and how should the sustained-release product be constructed? Our concern, therefore, is to examine the potential mechanisms available and to describe the general nature of the dosage form construction.

A. Repeat-Action Release and Continuous Release

To maintain the drug level at a constant desired value, we can employ frequent dosings of drug to generate a series of peaks and valleys in the blood level profile, whose mean value lies on the plateau of the ideal case. This approach is shown in Figure 2. The success of this approach depends on the frequency of the multidoses because, obviously, the more frequent the dose the smaller the peaks and valleys and the closer the extreme drug level will adhere to the plateau value. This is the approach taken with the Spansules, where four dosage units were employed in each Spansule. One dose unit provided drug in a nonsustained form to establish the initial blood level of drug and the other three doses were intended to release drug at 2-, 4-, and 6-h intervals. Depending on the drug properties, other intervals can be used, as can a greater number of repetitive doses, although more than four becomes impractical from a manufacturing standpoint.

An alternate approach is to employ a continuous release of drug. With this method, a nonsustained portion of the dosage form is needed to rapidly establish the therapeutic level of drug in the blood, and then by some suitable mechanism, drug is continuously provided in a zero- or first-order fashion. In this regard it is appropriate to comment on the drug concentration versus time profile for a system releasing drug via first-order kinetics. Contrary to the case where drug is released via zero-order kinetics, as depicted in Figure 1, first-order release produces a more or less bell-shaped profile. Whether the bell shape is symmetrical or skewed and whether it is narrow or wide depends on the drug and the sustained-release system employed; that is, the kinetics of release. Examples of this type of profile will be discussed and demonstrated later in the chapter.

B. Mechanisms of Sustained Release

A zero-order releas of drug is needed for the dosage form, which means that the rate of drug release is independent of drug concentration

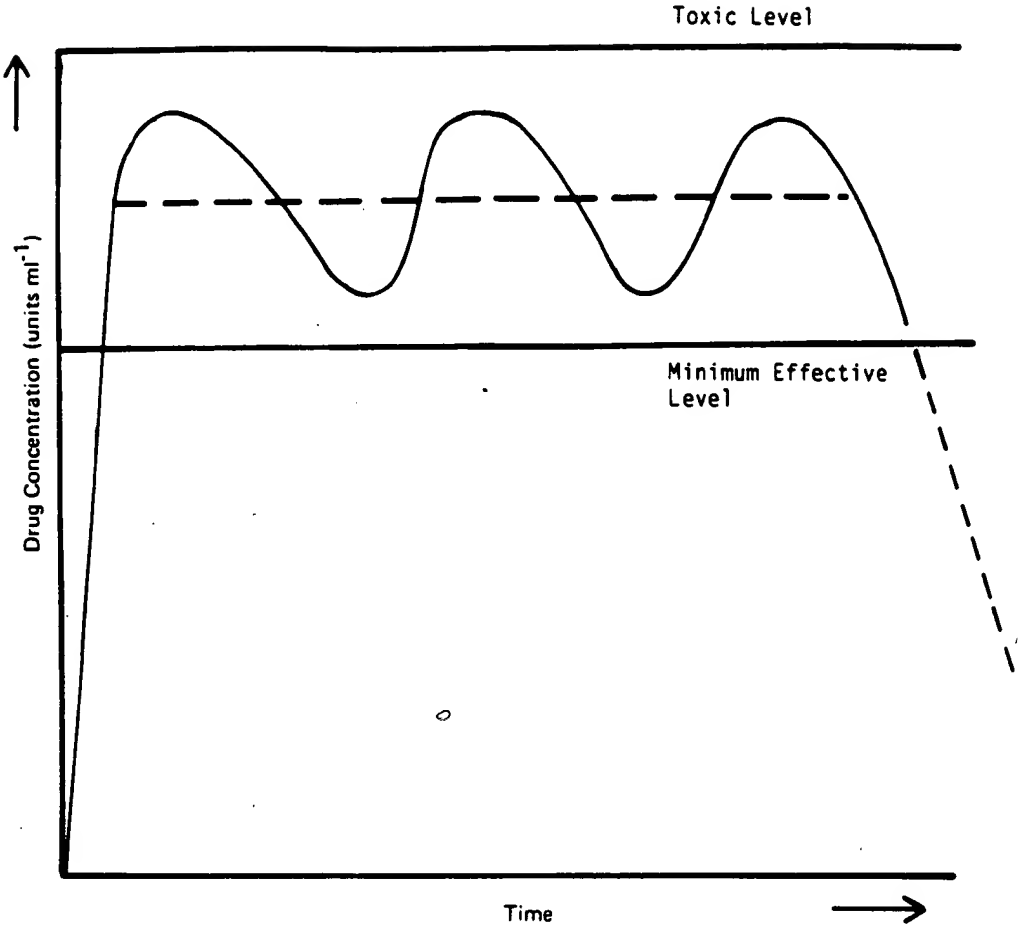


Figure 2 Repetitive release approach to sustained-release. The dotted line represents the ideal sustained-release profile.

$$\frac{dC}{dt} = k_r^0 \tag{5}$$

or expressed in amounts

$$\frac{dM}{dt} = k_r^0 \tag{6}$$

At times it is not possible to generate a constant-release product and a slow first-order release of drug is employed. A slow first-order release will approximate a zero-order release as long as only a fraction of drug release is followed [29]; that is, less than one half-lif is followed.

To attain a zero-order release rate, we have sev ral mechanisms and dosage form modifications that we can employ. We will r strict our coverage of potential mechanisms to those that can be mployed in the coating approach to sustained release.

Diffusion

A number of sustained-release products are based on diffusion of drug. The following discussion, although somewhat naive, will bring into perspective those properties that should be considered in the diffusion approach.

Fick's first law of diffusion states that drug diffuses in the direction of decreasing concentration across a membrane where J is the flux of the drug in amount/area-time.

$$J = -D \frac{dC}{dx} \tag{7}$$

where D is the diffusion coefficient in area/time, C is the concentration, and x is the distance. Assuming steady state, equation 7 can be integrated to give

$$J = -D \frac{\Delta C}{\ell} \tag{8}$$

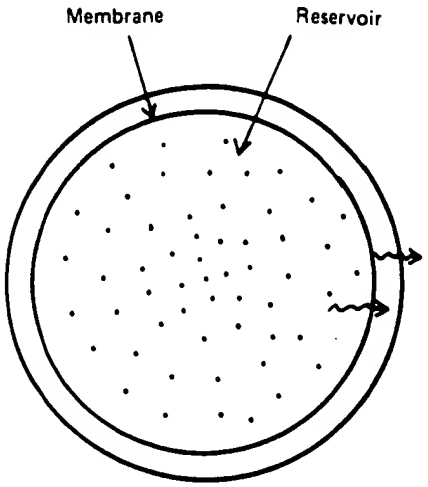
or expressed in more common form when a water-insoluble membrane is employed

$$\frac{dM}{dt} = \frac{ADK\ \Delta C}{\ell} \tag{9}$$

where A is area, D is diffusion coefficient, K is the partition coefficient of drug into the membrane, ℓ is the diffusional pathlength (thickness of coat in the ideal case), and ΔC is the concentration gradient across the membrane.

In order to have a constant rate of release, the right-hand portions of equations 8 and 9 must be maintained constant. In other words, the area of diffusion, diffusional path length, concentration increment, partition coefficient, and diffusion coefficient must be invariant. Usually, one or more of the above parameters will change in oral sustained-release dosage forms giving rise to non-zero-order release.

The more common diffusional approaches for sustained drug release are shown in Schemes 3 and 4. In most cases, the drug must partition into a polymeric membrane of some sort and then diffuse through the m mbrane to reach the biological milieu. When the tablet or microcapsule contains excess drug or suspension, a constant activity of drug will be maintained until the excess has been removed, giving rise to constant drug release. In Scheme 3 the polymer is water insoluble, and the important parameter is solubility of drug in the membrane, since this gives rise to the driving force for diffusion. In Scheme 4 either the polymer is partially soluble in water or a mixture of water-soluble and water-insoluble polymers is used. The water-soluble polymer then dissolves out of th film, giving rise to small channels through which the drug can diffuse. The small channels would presumably give a constant diffusional path length, and hence maintain constant conditions as described earlier. Although diffusion through the channels should be much more rapid than diffusion through th membrane noted in Scheme 3, it is possibl to have a situation wh reby membrane diffusion, being quite rapid in this case,

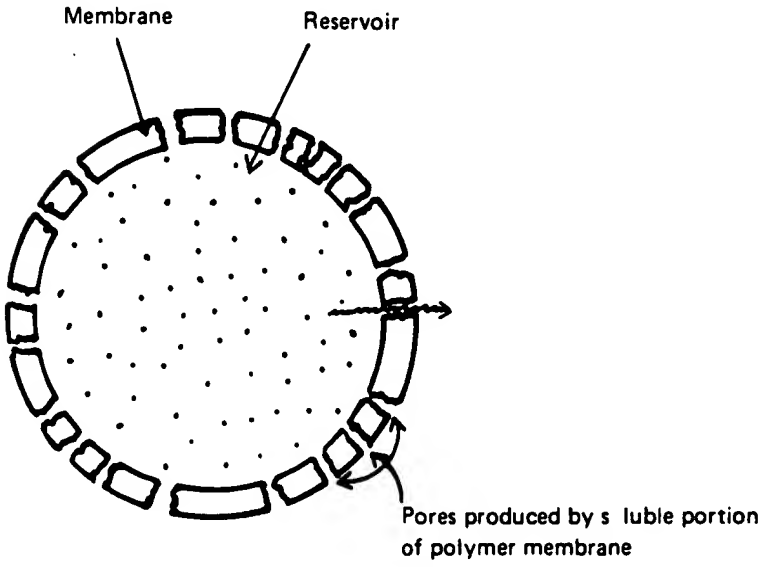


Scheme 3 Diffusion control of drug release by a water-insoluble polymer.

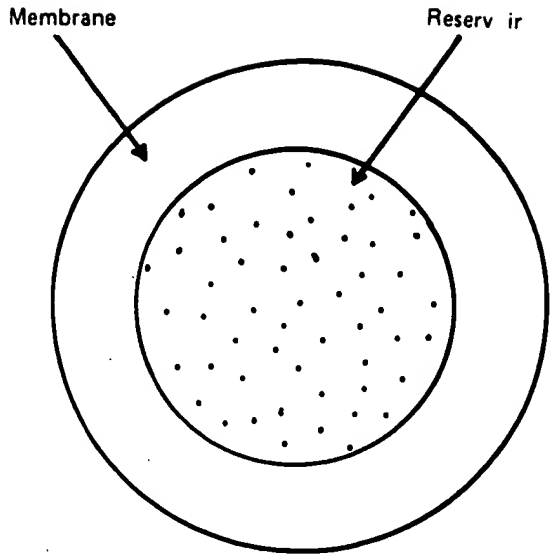
is within an order of magnitude of pore diffusion. In this event, both types of diffusion, membrane and pore, will provide contributions to the overall diffusion rate and the equations would have to be modified to account for these combined effects.

Dissolution

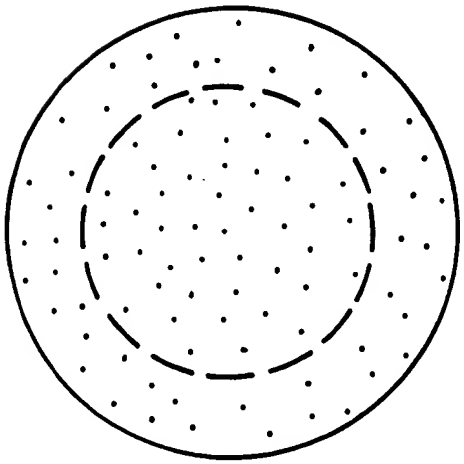
In this case, the drug is embedded (coated) in a polymeric material and the dissolution rate of the polymer dictates the release rate of drug. The



Scheme 4 Diffusion control of drug release by a partially water-soluble polymer.



Scheme 5 Dissolution control of drug release via thickness and dissolution rate of the membrane barrier coat.



Scheme 6 Dissolution control of drug release via polymer core erosion or polymer-coating erosion. (Note: Although equations are based on spherical tablets, erosion of conventional flattened tablets is similar but there is a combination of various R terms where R depends on the axis being measured. See Ref. 38. It is assumed that diffusion of water, metabolites, or biologically active components is not rate limiting.

drug release rate, if governed by erosion or dissolution, can be expressed as

$$\frac{dM}{dt} = A \frac{dx}{dt} f(C) \tag{10}$$

where (dx)/(dt) is the erosion rate, f(C) is the concentration profile in the matrix, and A is area. A constant erosion rate can produce zero-order release kinetics, provided the drug is dispersed uniformly in the matrix and area is maintained constant [36,37]. Oftentimes, swelling of the system or a significant change in area produces non-zero-order release.

The common forms of dissolution control are shown in Schemes 5 and 6. In Scheme 5 we have a barrier coat across a microcapsule or nonpareil seed containing drug, and the release of drug is dictated by the dissolution rate and thickness of the barrier coat. Varying the coating thickness, or layering concentric spheres of coating material and drug reservoir material, gives rise to different release times, producing the repeat action dosage form. Once the polymer has dissolved, all of the drug contained in the capsule or seed is available for dissolution and absorption. In Scheme 6 the drug is either embedded in a polymer or coated with a water-soluble polmyer, which in turn is compressed into a slowly dissolving tablet. The release rate is controlled by the dissolution rate of the polymer or tablet.

Osmosis

Placement of a semipermeable membrane around a tablet, particle, or drug solution, which allows creation of an osmotic pressure difference between the inside and outside of the tablet and hence "pumps" drug solution out of the tablet through a small orifice in the coat, can be used as a sustained-release mechanism. The key component of the system is the ability of a drug solution to attract water through a semipermeable membrane by osmosis. Since the drug solution is contained within a fairly rigid system, drug solution can be pumped out of the tablet or particle at a controlled constant rate if a small hole is created in the coating surface and a constant activity of drug, that is, excess drug, is maintained. Controlling the rate of water imbibition thus controls the rate of drug delivery. This can be seen in the following expression [12]

$$\frac{dV}{dt} = k \frac{A}{\ell} (\Delta\pi - \Delta P) \tag{11}$$

where dV/dt is the flow rate of water, k, A, and ℓ are the membrane permeability, area, and thickness, $\Delta\pi$ is the osmotic pressure difference, and ΔP is the hydrostatic pressure difference. Keeping the hydrostatic pressure small relative to the osmotic pressure, equation 11 reduces to

$$\frac{dV}{dt} = k \frac{A}{\ell} (\Delta\pi) \tag{12}$$

By maintaining the right-hand side of equation 12 constant, a zero-order release system will result.

COATING METHODS. Coating is a versatile process which imparts various useful properties to the product. Modifications of drug-release patterns such as enteric release, repeat-action release, and sustained release are the most important pharmaceutical applications of coating. Although many coating techniques, for various purposes, have been detail d in previous chapters, we have elected to discuss the coating methods for the purpose of modified release.

Pharmaceutical coatings have been classified into four basic categories: sugar coating, microencapsulation, film coating, and compression coating. Sugar coating of compressed tablets and granules is regarded as the oldest process, involving the multistage build up of sugar layers through deposition from an aqueous-coating solution and coating powder. Sugar coating falls outside the scope of this chapter owing to the inability to control drug release through a highly water-soluble sugar barrier.

A. Microencapsulation

Microencapsulation is a process in which tiny particles or droplets are surrounded by a uniform coating (so-called microcapsule) or held in a matrix of polymer (so-called microsphere). A number of microencapsulation techniques, including aqueous phase separation, three-phase dispersion, organic phase separation, and interfacial polymerization, have been used to encapsulate pharmaceuticals and to retard the liberation of drug from microcapsules.

Aqueous phase separation methods to prepare microcapsules include the simple coacervation of hydrophilic colloids with ethanol or sodium sulfate as dehydrating agents. In addition, one can employ a complex coacervation of two dispersed hydrophilic colloids of opposite electric charges with subsequent pH change. Aqueous phase separation was patented as an encapsulation process by Green in 1955 [39], and has been used commercially since that time for numerous applications.

The three-phase dispersion method involves dispersion of the materials to be coated in a nonsolvent liquid phase containing colloidal or film-forming materials such as gelatin. This two-phase system is then dispersed in a third phase by emulsification, through spraying or other means, and the coating material is gelled, usually by cooling. The resulting gelled droplets are then either separated and dried or partially dehydrated with an aliphatic alcohol and then separated and dried. Variations on this process have been used commercially to encapsulate oil-soluble vitamins such as vitamin A. One of the earliest applications of this method was reported in a British patent in 1938 [40].

Generally, aqueous phase separation and three-phase dispersion methods are used to encapsulate water-insoluble or poorly water-soluble materials which are usually poor drug candidates to incorporate into a sustained-release system. Gelatin is the most commonly used microencapsulating agent for the two processes described above. Even for poorly water-soluble drugs, gelatin is usually not able to achiev th desired dissolution profile owing to the hydrophilic properties of gelatin. The us of formalin in treatment to cross-link the gelatin and/or dual coating of gelatin microcapsules may be necessary to improv th dissolution profil . In addition, these encapsulation processes would b precluded for heat-sensitive materials and substances with a stability and/ r solubility problem at the pH of coacervation.

Nonaqueous phase separation involves dispersion of core material in an organic continuous phase in which the wall-forming polymer has been dissolved. Phase separation is induced by the addition of a nonsolvent, incompatible polymer, inorganic salt, or by altering temperature of the system. The organic phase separation method can be employed in the manufacture of microcapsules using various water-insoluble polymers as coating materials to enclose water-soluble drugs and to slow the drug-release rate.

Encapsulation via interfacial polymerization was pioneered by Chang [41,42] in work designed to produce artificial cells. This method involves the reaction of various monomers, such as hexamethylene diamine and sebacoyl chloride, at an interface between two immiscible liquid phases to form a film of polymer that encapsulates the dispersed phase. Capsules formed by interfacial polymerization usually have relatively thin semipermeable membranes highly suited for artificial cell studies or applications requiring permeable walls. This method may give rise to questions about toxicity of the unreacted monomer, the polymer fragments, and other constituents in the process, instability of the drug in the reaction medium during the polymerization period, fragility of the microcapsules, and high permeability of the coating to low molecular weight species [43]. Various other polymerization procedures, including bulk, suspension, emulsion, and micellar polymerization, have received considerable academic interest to entrap active materials in polymer matrices. However, inherent problems of polymerization procedures such as impurities in the system, limited drug solubility in the monomer, excessive drug degradation caused by reaction with the monomer or initiator, and possible entrapment of drug in polymers may prevent the pharmaceutical industry from actively engaging in this approach to control drug release.

In general, microencapsulation techniques using liquid as a process medium are rather complicated and difficult to control. Several process difficulties such as hardening of the capsule shell, isolating the microcapsules from the manufacturing vehicle, and drying the microcapsules to form free-flowing powder should be solved in order to ascertain batch to batch uniformity. Equipment required for microencapsulation by these methods is relatively simple: It consists mainly of jacketed tanks with variable speed agitation. The process can be carried out on a production scale with good reliability, reproducibility, and control. However, process control, product quality control, and scale-up problems appear to be the limiting factors influencing general acceptance by the pharmaceutical industry.

The most common mechanical microencapsulation process is the spray-drying technique, which consists of rapid evaporation of the solvent from the droplets. Spray-drying techniques may produce monodispersed free-flowing particles which can be directly compressed into tablets, filled into capsules, and suspended in water. However, the microcapsules obtained by spray drying tend to be very porous because of rapid volatilization of the solvent. Spray-congealing techniques accomplish coating solidification by thermal congealing of the molten coating materials such as hydrogenated castor oil, cetyl alcohol, monoglyceride and diglyceride, etc. Spray-congealed coatings are less porous but require coating materials that melt at moderate temperature.

Successful attempts using spray-drying and congealing techniques to control the release of sulfa drugs have been reported [44–47].

B. Film Coating

Film coating involves the deposition of a uniform film onto the surface of the substrate, such as compressed tablets, granules, nonpareil pellets, and capsules. Intermittent manual application or continuous spraying of coating solution onto a mechanically tumbled or fluidized bed of substrates allow the coating to be built up to the desired thickness. Because of the capability of depositing a variety of coating materials onto solid cores, this process has been widely used to make modified-release beads and tablets in the pharmaceutical industry.

Properly designed film coating can be applied to pharmaceutical products to achieve performance requirements such as rapidly dissolving coatings, sustained- or controlled-release coatings, and enteric coatings. The polymer(s) used in coating formulations is the predominant factor for the properties of the film coat. Water-soluble film formers such as methyl cellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyethylene glycol, polyvinyl pyrrolidone, etc., form a rapidly dissolving barrier. Enteric materials such as cellulose acetate phthlate, polyvinyl acetate phthalate, methacrylic acid ester copolymers, etc., form acid-resistant films. The hydrophobic water-insoluble polymers such as ethyl cellulose, cellulose acetate, cellulose triacetate, cellulose acetate butyrate, and methacrylic acid ester copolymers are used to extend the release of drug over a long period of time. Depending upon the physicochemical properties of the drug and the substrate formulation, several coating approaches have been employed to regulate drug release.

Partitioning Membrane

Partitioning membranes, continuous hydrophobic polymeric films which remain intact throughout the gastrointestinal tract, can be applied onto the coating substrate by using a single polymer or a combination of water-insoluble polymers. Since drug molecules cross the membrane by both a partition and a diffusion process, solubility of the drug in the polymeric material is a prerequisite to permeation. The polymeric material should be carefully selected to have the desired permeability to the drug and water in order to achieve the desired release profile. In addition to thickness of membranes, the permeability of the film can also be adjusted by mixing two water-insoluble polymers in any desired proportion.

Dialysis Membrane

Frequently, the partitioning membrane is too effective to regulate drug release. In other words, the drug within the coating would be released very slowly or be released not at all for a long period of time. The inclusion of hydrophilic additives within the coating along with hydrophobic polymer(s) creates pores when the additives are dissolved by water, which guarantees the penetration of water and elimination of drug entrapment. When the drug molecule leaves the membrane by diffusing through pores filled with dissolution media (dialysis mechanism) the siz of the drug molecules and solubility of the drug in a dissolution medium are important factors in transport. Some water-soluble additives such as sodium chloride, lactose and sucros have poor solubility in organic solvents and may be micronized and suspended in a solvent-based coating system. Water-soluble polymers such as methyl cellulose, polyvinyl pyrrolidone, and

polyethylene glycol are commonly mixed with hydrophobic polymers to regulate drug release owing to their excellent film-forming properties and solubility in organic solvents. In addition to film thickness, the ratio of soluble components to insoluble polymer in the coating influences the release rate. Porous membranes may also be prepared by incomplete coating of hydrophobic polymers. However, strict process control is necessary to ascertain the reproducibility owing to sensitivity to the coating weight.

Fat Wax Barrier

Mixtures of waxes (bees wax, carnauba wax, etc.) with glycerol monopalmitate, cetyl alcohol, and myristyl alcohol can be applied onto the substrate to form a barrier by hot-melt coating. Hot-melt coating is the most economical process owing to elimination of solvent cost and the inexpensiveness of the coating materials. However, a higher level of coating, compared to polymeric film coating, is normally required to retard the liberation of the drug.

Incorporation of Enteric Materials into the Formulation

In general, pH-independent dissolution is the ideal attribute of a controlled-release dosage form. However, most drugs are either weak acids or weak bases; their release from delivery systems is pH dependent. If the drug has a higher solubility in acidic than in basic media, enteric material may be incorporated into the rate-controlling barrier or core matrix to minimize the effect of pH-dependent solubility. In another approach, physiological acceptable buffering agents can be added to the core formulation to maintain the fluid inside the rate-controlling membrane to a suitable constant pH, thereby rendering a pH-independent drug release [48]. Enteric material also can be incorporated into rate-controlling membranes or core matrices to create pH-dependent release of the drug. The dosage form with pH-dependent dissolution characteristics may be beneficial in some cases to improve the extent of absorption by dumping the dose in time and preventing the unabsorbed dose being entrapped in the stool. Sustained-release preparations overcoated with enteric material can be utilized as an intestinal delivery system with sustained-release properties. Enteric-coated dosage forms can be overcoated with a drug layer to form a repeat-action preparation.

CORE PREPARATION. Very few drug particles possess adequate physicochemical properties for the usual coating process. These properties include (1) suitable tensile, compaction, shear, impaction, and attrition strengths to avoid destruction during the coating process; (2) approximately spherical shape to obtain good flow and rolling properties in the coating equipment; (3) suitable size and size distribution; and (4) suitable density to avoid escape of the drug particles during the coating process. Certainly, different types of coating equipment have their own capabilities to handle the cores, leading to different requirements of the cores for various equipment. For the pan coating process, a relatively large particle size (larger than 500 μm) and a spherical shape are generally considered necessary to provide excellent rolling in the coating pan and to avoid the agglomeration and/or aggregation owing to inefficiency of drying and long contact time among the cores. Although fluidized-bed coating

systems expanded coating capabilities dramatically, suitable strengths and weight of the cores are needed to avoid excessive attrition of drug particles and suction of drug particles into the filter during the coating process. The major advantages of using pure drug particles as coating substrates are elimination of the core-making process and a less bulky final product. Potassium chloride and acetyl salicylic acid crystals are typical examples which have been satisfactorily coated in a coating pan or a fluidized-bed coating system.

1. *Compaction process.* Apparently, tablets are the most common and easiest dosage form to coat. Tablets with excellent friability, hardness, and edge thickness are preferred for coating. However, sustained-release film-coated tablets may prematurely dose dump due to accidental rupture of the coating film. The use of a multiple-unit instead of a single-unit dosage form is a pharmaceutical trend because of the presumed reduction of the inherently large inter- and intrasubject variation linked to gastrointestinal transit time. Tablets of small dimensions have been successfully prepared from polyvinyl alcohol and subsequently cross-linked at the surface to form a quasimembrane-controlled system for a multiple-unit dosage form [49]. In order to achieve high output in large-scale manufacturing, this approach to the preparation of cores may face formulation difficulties and tablet tooling problems; i.e., multitipped punches. The limited size flexibility of the tableting method to manufacture cores for a multiple-unit device is another disadvantage.

Other methods with production capacity, such as slugging, chilsonator, and Hutt Compactor, can be used to produce granules in the compaction mode. However, irregular-shaped granules are commonly observed and extensive sieving is necessary to remove the fines and oversized granules.

2. *Surface-layering process.* Another common approach to core production involves the use of substrates and enlargement of the substrates by a surface-layering technique. Thus, nonpareil seeds of various sizes or sugar crystals are used as the substrate. Application of an active substance onto an inert substrate can be carried out by uniform coating in a rotating coating pan in the presence of a suitable adhesive. In detail, the substrate is uniformly wetted by manual spreading of a binding solution, followed by attachment of the active substance to the surface of the substrate. Commonly used adhesives include solutions of polyvinyl pyrrolidone polyethylene glycols, cellulose ethers, natural gums, shellac, zein, gelatin, and sugar syrup. Suitable binder(s) and solvent systems for the binder(s) must be found in order to have smooth production of cores without excessive agglomeration of the cores or separation of the drug particles. Enteric binders, such as cellulose acetate phthalate and shellac, may impart pH-dependent dissolution properties to the final product. Separating agents, such as talcum and magnesium stearate, may be used to eliminate or reduce tackiness of the adhesives. Trituration technique, to blend the potent drug with the auxiliary agents, is usually r - quired to obtain a uniform distribution of the drug onto the substrate surface.

The powder layering process requires a great deal of repetition, and is thus time consuming. Moreover, undesired agglomeration or aggregation and adhesion to the wall of coating equipment can occur. To avoid the labor-intensive powder layering process in a coating pan, a centrifugal-type fluidized bed with a powder feed device (CF-Granulator) has

been used to produce high-quality pellets. The stirring chamber of the CF-Granulator consists of a fixed specially curved wall stator and a directed rotating plate rotor. Fluidization air, through a gap slit between the stator and rotor, prevents the substrates from falling. The substrates are whirled up along the wall of the stator owing to centrifugal force of the rotor and to the upper part of the wall due to the fluidization air. Subsequently, they drop due to gravitational force. During the spiral stirring operation, layering powder is metered to the fluidized bed from a powder feed unit. A binder solution is sprayed from a spraying gun to cause binding of the powder to the substrate surface.

It is also possible to dissolve or to suspend the drug in the binder solution and to apply this liquid uniformly to the surface of the substrate using a coating pan or fluidized-bed system. However, there are several difficulties with this approach, including the tendency to clog the nozzle with the slurry. A large quantity of solvent may be needed to dissolve or suspend the active substance. In addition, drug loss to the air stream and possible adverse aggregation of the cores can occur. Another inherent disadvantage of the layering process is the possible formation of unduly large pellets owing to the use of nonpareil seeds as a substrate. Small-sized substrates, such as sugar crystals, can be used to eliminate bulkiness of the pellets. The finer the substrate, the finer the drug particle should be and the more difficult the process.

3. *Agglomeration process.* Alternatively, the drug particles in the powder bed can grow by wet agglomeration. The extent of granule growth depends on the amount of granulating solution, the type of binder, the force of agitation, and heat applied. The conventional wet granulation method to prepare the substrate for coating can give rise to problems such as irregular-shaped particles with a coarse and porous surface, soft and pliable particles, and a broad granular size distribution. Application of relatively large amounts of coating material may be required owing to capillary suction of the coating fluid to pores. The porous structure and irregular shape of the granules may lead to an unpredictable sustained-release coating. Additional powder layering to round off the granules into a sphere or to smooth surfaces or perhaps to increase the strength of the pellets may be important. However, Kohnle et al. [50] have successfully produced microspherules which are suitable for enteric- and sustained-release coating through agglomeration of fine drug particles by using a Twin Shell Blender with an intensifier bar assembly.

The inclined dish granulator or disc pelletizer is well known and highly utilized in the fertilizer, iron ore, and detergent industries. It also has been adopted throughout the pharmaceutical, chemical, food, and allied industries. The equipment, known as the nodulizer and pelletizer, are available for continuous production of spherical pellets. The unit normally consists of a shallow cylindrical dish, motor drive, adjustable scrapers, spraying system, and powder feed device. As the pan rotates about an inclined axis, the raw material bed is rolled by centrifugal force and maintained as a uniform deposit of material onto the base of the pan by a plow. Scrapers also prevent buildup of materials on the dish surface. Powdered ingredients must be milled, premixed, and deaerated in order to have a uniform chute fed to the unit. Powder materials are continuously metered to the pan at a specific location, normally at a point three-fourths of a radius unit from the top of the dish. The spray angle depends to a large extent on positioning of the sprays and their distance

from the bed powders; commonly, a 60 spray angl is used. The spray droplet size should be adjusted according to feed size and desired granule size. In other words, if small granules are desired, a fine droplet spray should be used and vice versa. Also, the finer the feed material, the finer the spray droplet.

There are several theoretical equations that can be used to calculate the rotational speed of the pan. However, appreciable discrepancy exists in theory and practice. Usually 20–30 rpm seems a reasonable rotation speed. Following agglomeration, the finished granules are raked over by the dish rim, and the rim height can be adjusted to control granule size. Pronounced size segregation is the principal feature of dish granulation. This ensures almost perfectly spherical pellets with a narrow particle size distribution. Important parameters in the dish pelletizer include powder feet rate, position of powder feed chute, spraying rate, position of the spraying gun, spray nozzle size, angle of inclination, rotational speed, rim height, powder bed depth, and pan size. These variables interact to some extent to produce the final granules.

However, the noncontinuous granulation process in which spraying and drying stages are alternately repeated has been employed to maintain constant moisture levels and to produce high-density granules. A high level of perfection in shape and size of the granules cannot be obtained by agglomeration mechanism using a conventional fluidized-bed granulator. Recently, modified fluidized-bed units, such as the Roto-Processor, the Spir-A-Flow, and the Glatt Rotor Granulator/Coater, all utilize a rotating disc at the bottom of a fluidized-bed, replacing the air-distribution plate. This modification supposedly combines the advantages of the dish granulator and the fluidized-bed granulator. It has been demonstrated that the rotary fluidizer-bed granulator can be used to produce spherical granules with high density by an agglomeration mechanism [51]. In general, the layering mechanism using nonpareil seeds or sugar crystals as a substrate to build spherical-shaped pellets is relatively easy compared to the agglomeration mechanism.

4. *Extrusion-spheronization process.* Spherical pellets can also be produced using an extrusion-spheronization process. The main processing steps include (1) dry blending, (2) wet granulation, (3) kneading, (4) extrusion, (5) spheronization, (6) drying, and (7) screening. A thoroughly wet granulation containing the drug, diluent, and binder is forced through a radial or axial extruder with a suitable die design, such as a perforated die or multiple-hole die, by means of a screw feeder to produce roughly cylindrical extrudates. The extrudate size and final pellet size are determined by the size of the die used on the extruder. The pellet mill, a radial extruder, was initially developed for the agricultural industry to densify and upgrade the particle size of poultry and animal feeds. In operation, the preconditioned material is fed continuously in a controlled fashion to the pelleting chamber. The motor-driven outer perforated die ring causes the roller(s), which is mounted inside the die ring, to turn. The feed, carried by the rotation of the die ring, is compressed and forced through the holes in the die ring. As pellets are extruded, a knife, or knives, mounted at the exterior of the die ring, cuts the pellets to length. Application of the pellet mill to pharmaceutical products has been extremely limited. However, it deserves special mention owing to its ability to produce pellets with high density and low friability at a high output.

The extruded granules can be converted into consistently sized spheres by use of a Japanese device called a marumerizer or an English version of the device called a spheronizer. This device consists of a stationary cylinder with a smooth wall and a grooved rotating disc. The centrifugal and frictional forces, generated by the rough rotating baseplate, spheronize and densify the extruded granule. A typical time for the spheronization process would be approximately 5 min per batch, depending upon the nature of the material. Recently, a unique device called the Roto-Coil has been designed as a continuous spheronizer with no moving parts. This device consists of a spiral-shaped pipe. The extrudate is spheronized by passing through the pipe in a rotation movement with the aid of negative pressure generated by a fluidized-bed system. The advantages of the extrusion-spheronization process include: (1) production of the spherical pellets without using seeds, leading to reduction of the bulk of final product; (2) the ability to regulate size of the pellets within a narrow particle size distribution; (3) the ability to produce high-density, low-friability, spherical pellets; and (4) the ability to achieve excellent surface characteristics for subsequent coating, leading to an homogeneous distribution of coating material(s) onto the spherical pellets.

It is also possible to agglomerate the finely divided solids into spherical matrices from a liquid suspension [52]. In the spherical agglomeration process, fine powders are dispersed in the liquid. With controlled agitation, a small amount of a second liquid, which is immiscible with the first liquid and preferentially wets the solids, is added to induce formation of dense, highly spherical agglomerates. Another approach to prepare spherical matrices in the liquid state is the instantaneous cross-linking of drug-containing droplets of aqueous solution of sodium alginate in a suitable hardening bath, such as calcium chloride solution. This entrapment technique in recent years has become the most widely used method for immobilizing living cells and enzymes. It enjoys several advantages, such as a simple production process, a wide size range of beads, and a narrow size distribution [53]. The spray-drying process has been used to produce a spherical matrix. However, the spray-dried cores may be porous and fluffy because of rapid volatilization of the solvent. The spray-congealing process, also called the prilling process, is well known in the fertilizer industry for production of urea pellets and ammonium nitrate pellets. This process can be defined as the process by which a product is formed into particles, usually of spherical shape, by spraying a melt of the product into a chamber of suitable configuration through which cooling air is passed. The process is fairly restricted to matrix materials having suitable properties; namely, a high melting point and low heats of crystallization [54]. These several techniques may have potential applicability to produce spherical cores containing drug for subsequent sustained-release coating, and thus deserve further investigation. The physical properties of the product, such as pellet size and size distribution, pellet density, strengths, globocity, pore and pore distribution, etc., are different for various methods and may be important for subsequent coating as well as in product performance. Table 3 summarizes the various possible methods to core production and some selected pharmaceutical examples.

LATEX/PSEUDOLATEX COATING. The strict air-quality controls instituted by different federal agencies, spiraling solvent costs, the high price of solvent recovery system, and potential toxicity as well as to some

Table 3 Possible Methods for Core Manufacture and Some Selected Pharmaceutical Examples

Method and example	Equipment	Drug	Carrier binder	Comments and variable studied
Crystallization	Oslo crystallizer	Potassium chloride acetyl salicylic acid, etc.	N/A	Very few drug crystals possess adequate properties for coating.
Compressed tablet	Tablet press	Various	Various	Single-unit device. The accidental rupture of the film barrier may cause premature dumping of drug.
Min-Tablet [49]	Tablet press	Diprophylline	Polyvinyl alcohol	Relatively large matrices for multiunit device.
Granular	Chilsonator, Hutt Compactor	Various	Various	Irregular shaped granules. Extensive screening and recycling of undesired granules.
Layering [55]	CF-Granulator	Theophylline, pseudoephedrine hydrochloride, diphenhydramine hydrochloride	Gelatin, sodium carboxymethylcellulose, Kaolin/ Eudragit E-30D, Povidone	Evaluation of CF-Granulator for pelletization.
Layering [56]	Fluidized-bed coater	Dexamphetamine sulfate	Gelatin	As cores for hot-melt and cellulose acetate phthalate coating to obtain sustained reslease and enteric properties.

Layering [57]	Coating pan	Sodium salicylate	Ethyl cellulose	As cores for fluidized-bed coating to obtain a product with enteric and sustained-release properties.
Agglomeration [58]	Planetary mixer, high shear mixer	Hydrochlorothiazide	Microcrystalline cellulose	
Agglomeration [50]	P.K. Blender with intensifier bar	Aspirin, caffeine, phenylephedrine hydrochloride, chlorpheniramine maleate	Povidone	Extensive screening and recycling of undesired granules.
Agglomeration [59]	Dish granulator	N/A	Maize starch	Evaluation and studies of operating conditions for the formation of pellets.
Agglomeration [51]	Rotary fluidized bed	Butalbital	Lactose, corn starch, and povidone	Comparison of rotary fluidized-bed granulator with conventional fluidized-bed granulator.
Agglomeration [58]	Rotary fluidized bed	Hydrochlorothiazide	Microcrystalline cellulose	
Extrusion-spheronization [60]	Extruder and marumerizer or spheronizer	N/A	N/A	General description and discussion of extrusion spheronization technology.
Extrusion-spheronization [61]	Extruder and marumerizer or spheronizer	Dibasic calcium phosphate, magnesium hydroxide, sulfadiazine, acetoaminophen	Microcrystalline cellulose	Comparison of extrusion-spheronization process with conventional wet granulation.

Table 3 (Continued)

Method and example	Equipment	Drug	Carrier binder	Comments and variable studied
Extrusion-spheronization [62]	Extruder and marumerizer or spheronizer	N/A	Microcrystalline cellulose, sucrose, lactose	Effect of the spheronization processing variables, dwell time and speed, on the final granule properties.
Extrusion-spheronization [63]	Extruder and marumerizer or spheronizer	Acetoaminophen	Microcrystalline cellulose	Effects of spheronization processing variables including water content, extrusion speed, screen size, spheronizer speed and spheronizer time on tablet hardness and dissolution rate.
Extrusion-spheronization [64]	Extruder and marumerizer or spheronizer	Theophylline, quinidine bisulfate, chlorpheniramine maleate, hydrochlorthiazide	Microcrystalline cellulose, sodium carboxymethylcellulose	Effect of different diluents and drug-diluent ratio on the final granule properties.
Extrusion-spheronization [65]	Extruder and marumerizer or spheronizer	Acetoaminophen	Microcrystalline cellulose, carboxymethylcellulose	Use of factorial design to evaluate granulations prepared by extrusion-spheronization.
Extrusion-spheronization [66]	Extruder and marumerizer or spheronizer	N/A	Lactose, dicalcium phoshydrate povidone and microcrystalline cellulose	Elucidation of the factors that influence migration of solvent-soluble materials to the surface of beads made by extrusion-spheronization.

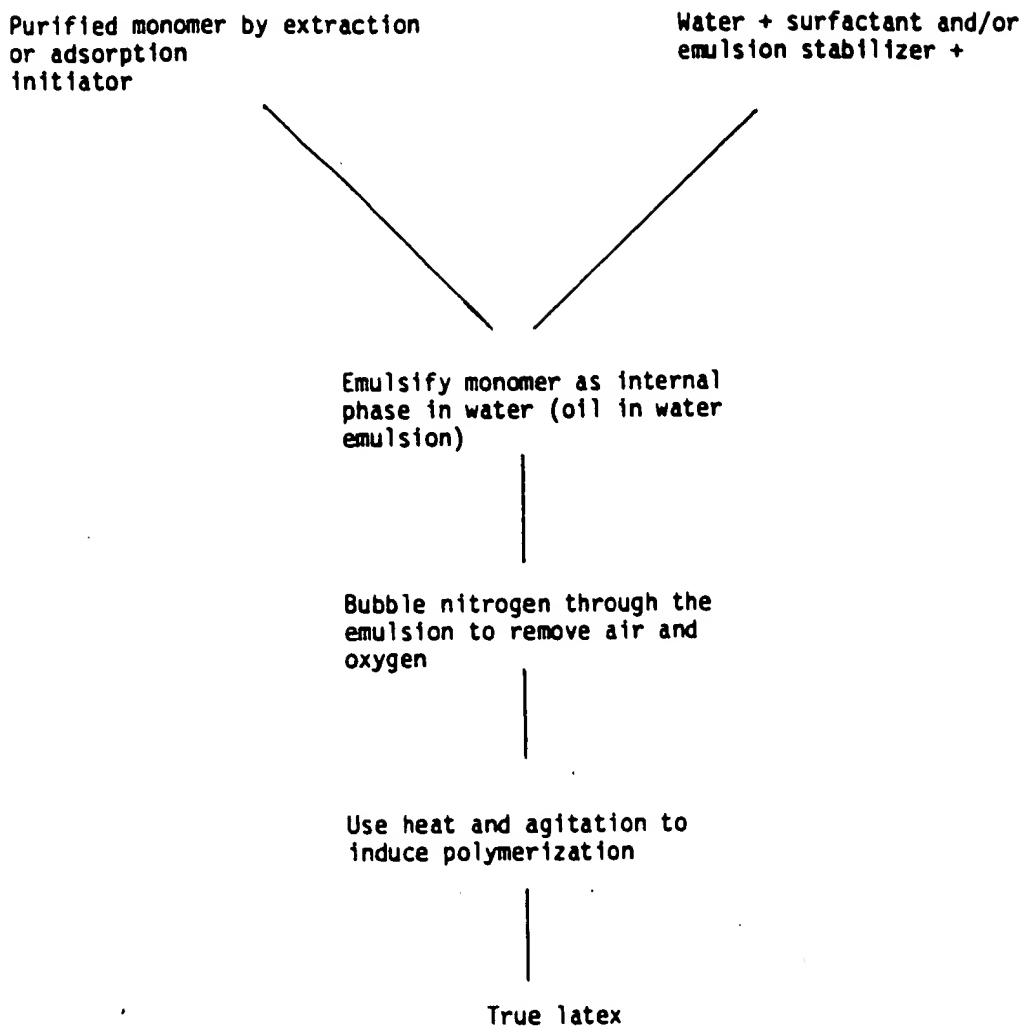
Extrusion-spheronization [58]	Extruder and marumerizer or spheronizer	Theophylline, quinidine sulfate, chlorpheniramine maleate, hydrochlorothiazide	Microcrystalline cellulose	Microcrystalline cellulose has excellent binding properties for granulation to be spheronized.
Spherical-agglomeration [52]	Liquid agitator	Sulfamethoxazole, sulfanilamide	White beeswax, ethylcellulose	Parameters affecting the size and release behavior of resultant matrix.
Gellation [53]	Dripping device and calcium chloride solution as a hardening agent	Enzymes and living cells	Calcium alginate	Widely used method for immobilizing living cells and enzymes. Possible pharmaceutical application for pellet making.
Gellation	Dripping device and coolant liquid	Diphenhydramine chloride	Gelation, glycerin	
Spray congealing [67,54]	Spray congealer	N/A	Materials with high melting point and low heats of crystallization	Variables affecting the spray congealing process, and possible pharmaceutical application for pellet making.

extent explosiveness and danger of these solvents have giv n pharmaceutical and food supplement processors considerable incentive to remov organic solvents from the coating process. The most commonly used methods to eliminate organic solvents are presented in Table 4. At present and in the foreseeable future, latex or pseudolatex coatings appear to be the best choice to eliminate solvent-based coatings for controlled drug release. Several techniques, including emulsion polymerization, emulsion-solvent evaporation, phase inversion, and solvent change, can be employed to prepare suitable latex/pseudolatex dispersion systems. Each method has advantages and disadvantages based upon ease of preparation, latex stability, convenience of use, film properties, and economics.

METHODS TO PREPARE LATEX DISPERSIONS

1. *Emulsion polymerization.* Polymerization in an emulsion state can be applied to a wide variety of vinyl, acrylic, and diene monomers with water solubility in the proper range, usually 0.001–1.000% [89–91]. The basic formula used in emulsion polymerization consists of water, monomer, surfactant, and initiator. The system contains three phases: Water containing small amounts of dissolved surfactant and monomer, monomer droplets stabilized by surfactant, and much smaller surfactant micelles saturated with monomer. The initiator decomposes into free radicals which react with monomer units at three possible sites for polymerization. The radicals can react with dissolved monomer in the aqueous phase, or can diffuse into the monomer droplets or the micelles. Obviously, there is very little initiation in the aqueous phase owing to low monomer concentration in the water phase. The diffusion rate of the radicals, which is directly proportional to surface area, is far greater into the micelles, and thus there is virtually no initiation in the monomer droplets. Free radicals, from initiator decomposition, begin polymerization in the monomer solubilized in the micelles. The micelles transform into growing particles. As these monomer-polymer particles grow, they are stabilized by more surfactant at the expense of uninitiated micelles, which eventually disappear. The growing latex particles are continually supplied with monomer by diffusion through the aqueous phase from monomer droplets. The latter gradually decreases in quantity as polymerization proceeds, until at a conversion of about 60%, they disappear completely. All free monomer has then diffused into the latex particles. The polymerization rate decreases as the monomer in the particles is depleted by further polymerization. The schematic process for emulsion polymerization is shown in Scheme 7.

2. *Emulsion–solvent evaporation technique.* The emulsion–solvent evaporation technique [92–97] also called emulsion hardening, has been widely used to prepare microspheres for controlled drug release [98–100]. The technique involves dispersion of drug in an organic polymer solution, followed by emulsification of the polymer solution in water. After continuous stirring, the solvent evaporates and drug-containing rigid polymer microspheres are formed. The procedure for preparing pseudolatex is essentially the same as that described above (Scheme 8). The polymer emulsion, with droplets so small they ar below the resolution limit of the optical microscope, can be accomplished by subjecting the crude emulsion to a source of energy such as ultrasonic irradiation or by passing the crude emulsion through a homogenizer or submicron dispenser. The polymer solvent is normally stripped from the emulsion at elevated temp ratures and pressures to leave a stable pseudolatex. If foaming is not a problem, the solvent may be removed under reduced pressure.



Scheme 8

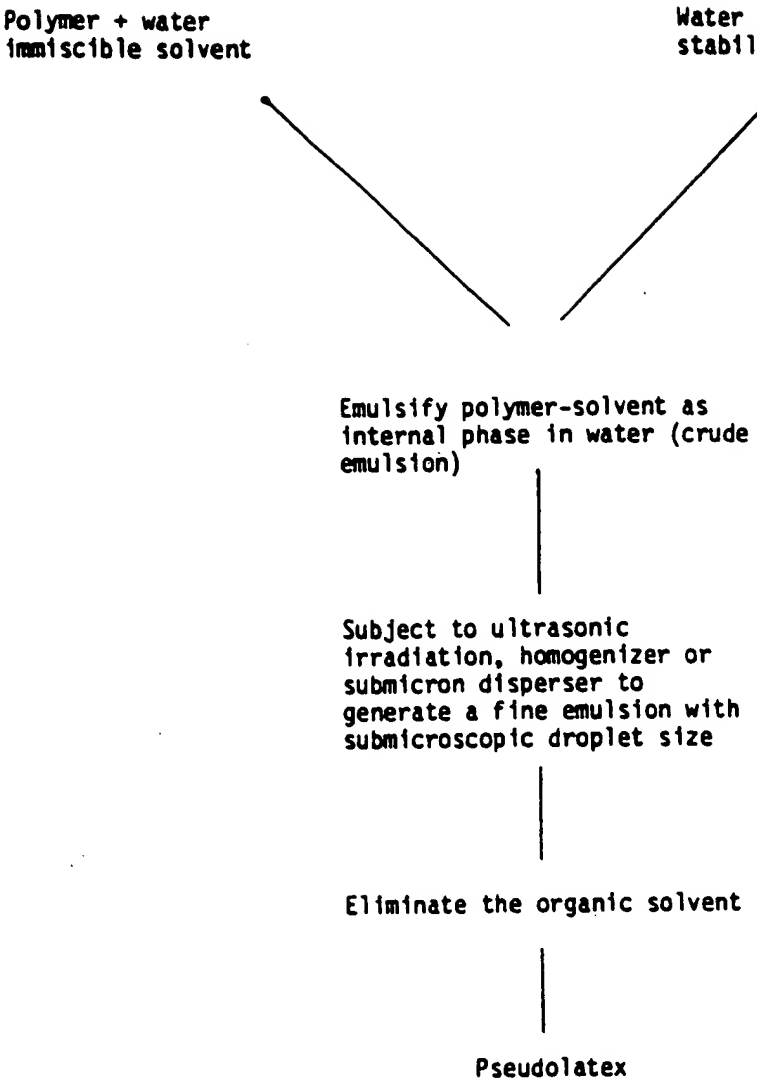
3. *Phase inversion technique.* The phase inversion technique [101–104] involves a hot-melt or solvent gelation of the polymer, which is then compounded with a long-chain fatty acid such as oleic acid, lauric acid, or linoleic acid using conventional rubber-mixing equipment such as an extruder. When the mixture is homogeneous a dilute solution of an alkali is slowly added to the mixture to form a dispersion of water in polymer. Upon further addition of aqueous alkali under vigorous agitation, a phase inversion occurs and a polymer in water dispersion is produced (Scheme 9).

4. *Solvent change and self-dispersible technique.* An ionic water insoluble polymer, which may be generated by acid-base treatment or chemical introduction of functional groups, such as ammonium groups, phosphonium, or tertiary sulfonium groups, may be self-dispersibl in water without any need for additional emulsifier [105,106]. Generally, the polymer is first dissolved in a water-miscible organic solvent or in a mixed water-miscible organic solvent system. The pseudolatex can then be obtained by dispersing the polymer solution in deionized water into

Table 4 Common Methods to Eliminate Organic Solvents in the Coating Process

Method	Function	Examples of coating materials	Comments
Compression coating	Compressible materials	Sugars, hydroxypropylmethylcellulose, polyvinyl alcohol	Totally eliminates organic solvents. It is not well accepted by pharmaceutical industry owing to complicated mechanical operation and formulation problems.
Aqueous solution	Water-soluble film formers	Methylcellulose, hydroxypropyl cellulose, hydroxypropylmethylcellulose	Film formers giving solutions of low viscosity are the most suitable for use. Totally eliminates organic solvents, but unusitable for controlled drug release.
Mixed organic aqueous system [68]	Enteric materials	Polyvinyl acetate phthalate, carboxylmethylethylcellulose, hydroxypropylmethylcellulose acetate phthalate.	Partially eliminates organic solvents. May be suitable for enteric coating, but not practical for controlled drug release.
Alkali salts [69,70]	Enteric materials	Shellac, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate.	To form gastric fluid resistant coatings, a volatile neutralizing agent, ammonium hydroxide or morpholine, is preferable to neutralize the enteric materials. Totally eliminates organic solvents.

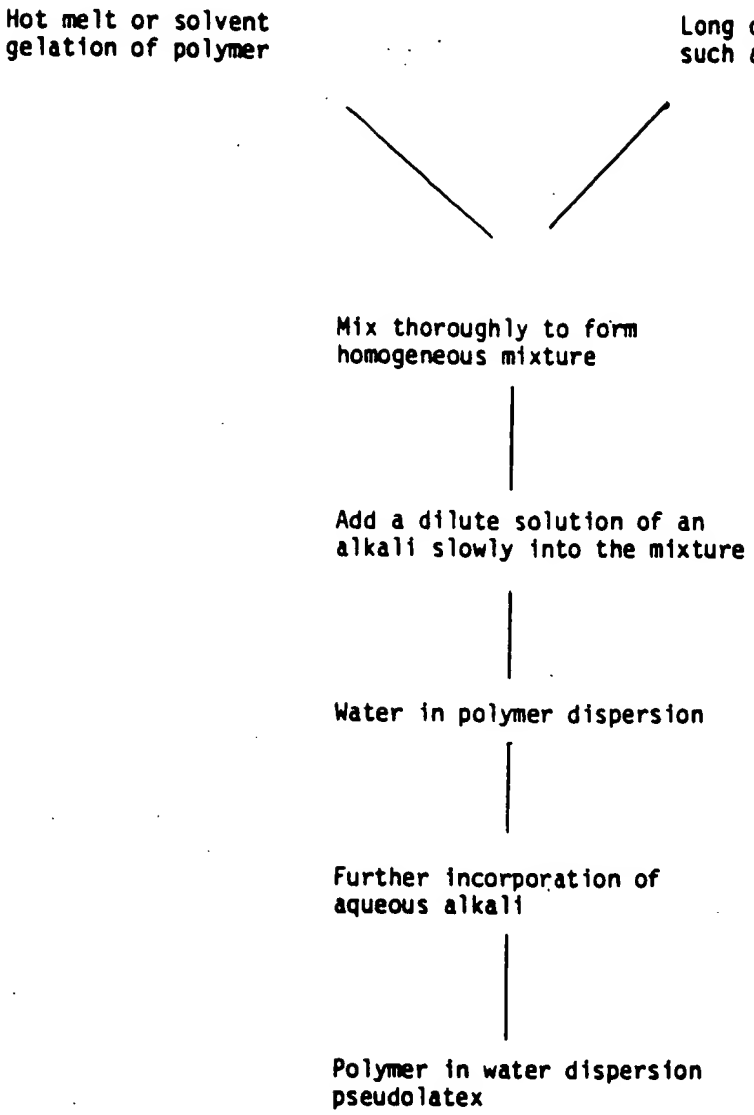
Hot melts	Materials with low melting point	Hydrogenated oil, wax, solid polyethylene glycol	Organic solvents can be eliminated completely. However, organic solvents may be needed to thin the hot melts, in some cases. Heating devices such as steam jackets or heating tape is needed for the spraying system to avoid solidification of the coating material. Ladle process may be more practical, less troublesome.
Aqueous dispersions of waxes and lipids [71]	Waxes and lipids	Castor wax, carnauba wax, Cutina HR, Hoechst Wax E, Durkee 07	Totally eliminates organic solvents. Aqueous dispersions of waxes and lipids may not be superior to hot melt coating.
Coating emulsions	Almost all water-insoluble polymers	Cellulose acetate phthalate, hydroxypropylmethylcellulose	Partially eliminates organic solvents. Still in their infancy as pharmaceutical coatings.
Latex dispersions [73–80]	Almost all water-insoluble polymers	Ethylcellulose pseudolatex, Eudragit RL/RS pseudolatex, Eudragit E-30D latex	Totally eliminates organic solvents. Latex dispersions usually have low viscosity and a high solids content. Latex systems have some applications in ophthalmic delivery systems [81], injectable colloidal delivery system [82], and molecular entrapment techniques for sustained-release dosage forms [83–88].



Scheme 8

the polymer solution under mild agitation. The organic solvent(s) is subsequently eliminated from the aquous-organic solution to leave a stable latex (Scheme 10). The absence of emulsifiers has several interesting consequences, such as stability to heat and mechanical shear, and dilutability with organic solvents. Table 5 lists the general features of four commercially available latex-coating systems for controlled drug release. Recently, latex/pseudolatex coating has been further expanded to use cellulose ac tate pseudolatex for elementary osmotic pumps [107] and water-based silicone elastomer dispersion for controlled-releas tabl t coating [108,109].

Th aforementioned techniques also can be used to prepare latex or pseudolatex of enteric polymers. Because it is costly to ship aqueous dispersions and some enteric materials are susceptible t hydrolysis, spray- or freeze-drying techniques may be used to dry aqueous polymeric

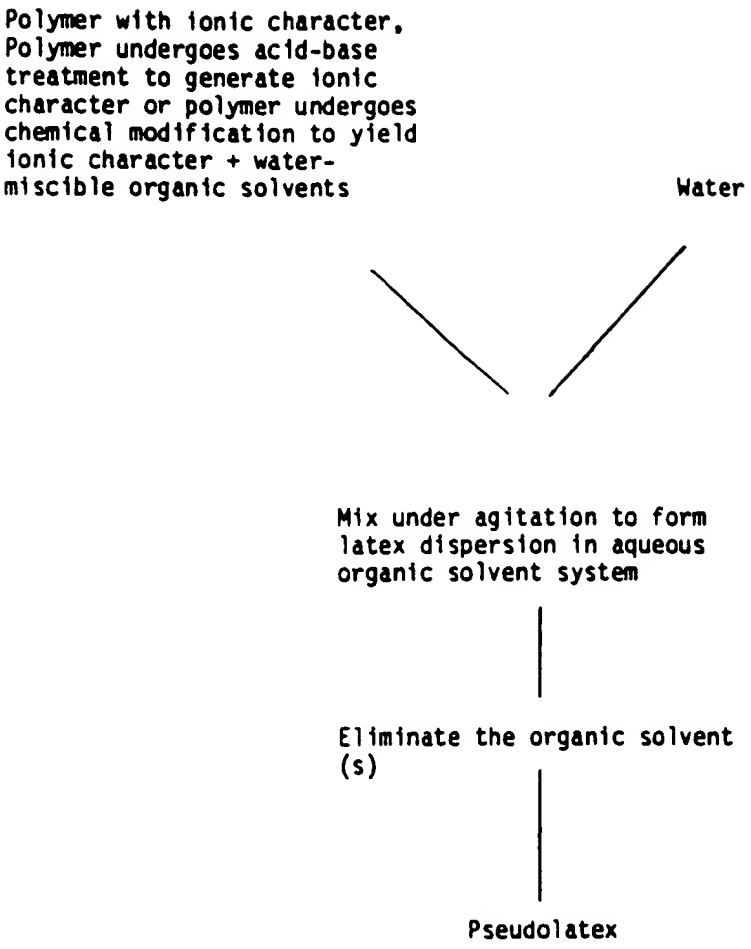


Scheme 9

dispersion and form a redispersible aqueous enteric coating system. Table 6 lists the general features of three dispersible aqueous enteric-coating systems.

Basic Considerations in Coating and Accessory Coating Equipment

COATING EQUIPMENT. A perforated pan as well as a conventional coating pan equipped with hot air supply, spray system, pan baffles, and variable coating pan speed can be used for latex coating. However, the relative inefficiency of drying and longer contact time in the coating pan may cause penetration of water into the core and thus discontinuity or irregularity of the film [110]. In the past 10 years, there has been a significant increase in the use of fluid-bed technology to granulate materials for improved compression and to coat cores for desired properties such as controlled drug release, enteric release, appearance, or taste masking. Fluid-bed coating using



Scheme 10

centrifugal-type or Wurster column-type equipment provides ideal conditions, such as rapid surface evaporation, controllable inlet air temperature, and short contact time, for latex coating.

ACCESSORY EQUIPMENT

1. *Nozzle systems.* Characteristics of three different types of nozzle are listed in Table 7 [111]. The ultrasonic nozzle is a relatively new and entirely different type of atomizing nozzle that offers several advantages over conventional nozzles. However, application of ultrasonic nozzles is still in its infancy. Thorough investigations are necessary to dedermine the feasibility of their pharmaceutical applications. Hydraulic guns are sometimes used in plac of air-atomizing nozzl s for large film-coating processes. The nozzles tend to clog with latex coating becaus the airless system generates a shear which may coagulat th formulated latex. Pneumatic nozzles have been adapted for fluid-bed systems, and have been shown to be an acceptable nozzle system for latex coating. The atomizing air is exposed to the product and, therefore, must be free of oil and other contaminants.

Table 5 General Features of Four Latex Coating Systems for Controlled Drug Release

Latex system	Method	General features
Eudragit E-30D (Rohm Pharma)	Emulsion polymerization	Poly (ethylacrylate, methylmethacrylate) latex, 30% w/w solid content. No plasticizer is required. May contain residual monomer, initiator, surfactants, and other chemicals used in the polymerization process.
Aqua-Coat (F.M.C. Corp.)	Emulsion-solvent evaporation	Unplasticized ethyl cellulose dispersion. Contains sodium lauryl sulfate and cetyl alcohol as stabilizers. 30% w/w solid content.
Surelease (Colorcon, Inc.)	Phase inversion	Fully plasticized ethyl cellulose dispersion. Contains oleic acid, dibutyl sebacate, fumed silica, and ammonia water, 25% w/w solid content.
Eudragit RS30D and RL30D (Rohm Pharma)	Self-dispersible	Unplasticized poly (ethylacrylate, methylmethacrylate, trimethylammonioethylmethacrylate-chloride) dispersions. Contains no emulsifiers. 30% w/w solid content.

Table 6 General Features of Three Dispersible Aqueous Enteric Coating Systems

Coating system	Method	General features
Aquateric (F.M.C. Corp.)	Emulsion-solvent evaporation followed by spray dry technique	Redispersible cellulose acetate phthalate coating system. Contains polyoxypropylene block copolymer and acetylated monoglycerides. Plasticizer is required.
Coateric (Colorcon, Inc.)	Mechanical means to reduce particle size of the polymer	Completely formulated dispersible polyvinyl acetate phthalate coating system.
Eudragit L-100-55 (Rohm Pharma)	Emulsion-polymerization followed by spray dry technique	Redispersible poly (ethyl acrylate–methacrylate acid) coating system. Contains polyvinylpyrrolidone, polyoxyethylene sorbitan fatty acid ester, and polyethylene glycol. Plasticizer is required.

Table 7 Nozzle Characteristics by Type

	Ultrasonic nozzles	Hydraulic (pressure)	Air atomizing (two fluids)
Principal of operation	Ultrasonic energy concentrated on atomizing surface, causes impinging liquid to disintegrate into a fog of microdrops	Pressurized liquid is forced through orifice. Liquid is sheared into droplets.	High-pressure air or gas mixes with liquid in the nozzle: Air imparts velocity to liquid which is then ejected through an orifice
Average microdrop size	20–50 μ (depending on frequency)	100–200 μ at 100 psi (higher pressure reduces size)	20–100 μ (air pressure fr m 10–100 psi)
Spray velocity variability flow rate	Low: 0.2–0.4 ms. Infinity variable from zero flow to rated capacity	High: 10–20 m/s ± 10% of specified rating	High: 50–20 m/s. Infinitely variable from 20% of maximum capacity to maximum
Minimum achievable flow rate	0 gph	0.5 gph	0.3 gph
Maximum achievable flow rate	30–40 gph	No limit	No limit
Orifice size/cloggability	Large: up to 3/8"—uncloggable	Very small, usually subject to clogging	Very small, usually subject to clogging

2. *Pumping systems.* Peristaltic or gear pumps are used in combination with nozzles to form a spray system. Th ability of a pumping system to deliver the coating liquid at the required rate for the duration of the coating cycle is critical for a uniform coating. A flow integrator can be used to eliminate pulsation of output flow which may cause uncontrolled wetting disruption of the spraying process.

3. *Humidity control.* In order to maximize the drying efficiency of the fluid-bed machine, it may be necessary to dehumidify the inlet air. Furthermore, the amount of moisture in the inlet air can significantly influence batch-to-batch variability of the coating process. Therefore, it is important to control ambient air humidity in the coating operation.

PROCESS VARIABLES

1. *Fluidization air temperature.* Film formation from a solvent-based system is dependent upon the entangling and packing of polymer molecules as the solvent evaporates. Relatively low fluidization air temperatures should be used to prevent spray drying of coating materials because of low heats of vaporization for commonly used solvents. The mechanisms of film formation from a latex system involves the softening of latex spheres caused by plasticization and/or temperature, the contact of latex spheres resulting from loss of water, followed by deformation and coalescence of the latex spheres owing to capillary force and surface tension of the polymer to form a continuous film [112]. The temperature of the inlet air has a dual function; to evaporate water and to soften and coalesce the latex spheres. Latices, as contrasted to aqueous solutions, have a very low affinity for water, and therefore relatively low temperatures can be used to efficiently evaporate water. However, column temperature is critical for latex softening and coalescence. In order to generate a continuous film, the column temperature must be higher than the minimum film-formation temperature. If the temperature is too high, it may cause excessive drying and softening of the latex film, and hence result in electrostatic interaction and agglomeration problems. Minimum film-formation temperature [113] should be used as a guideline to select the temperature of the inlet air. The glass-transition temperature [114] and film-softening temperature [76] can also provide useful information for choosing the column temperature.

2. *Spray rate.* The liquid spray rate affects the degree of wetting and droplet size. At a given atomization air pressure, increasing the liquid spray rate will result in larger droplets and a higher possibility to overwet the coating substrates. Slowing the spray rate may cause electrostatic problems owing to low bed humidity, especially at high temperature settings.

3. *Volume of the fluidized air.* Since a sluggish or vigorous fluidization can have detrimental effects on the coating process, such as side-wall bonding and attrition of core substrates, proper fluidization should be maintained throughout the coating process.

4. *Atomization pressure.* Atomization pressure affects the spraying pattern and droplet size. Excessive high atomization pr ssure may result in the loss of coating materials and breakage or attrition of the substrates. Excessive low atomization pr ssure may overwet the core and cause sid - wall bonding.

FORMULATION VARIABLES

1. *The nature of the plasticizer.* There are many plasticizers that are compatible with ethyl cellulose and polymethyl methacrylate and can be used for plasticization [115]. For the polymer with a relatively high glass-transition temperature, a plasticizer with a strong affinity to the polymer must be found in order to form a resistant film. Plasticizers with low water solubility are generally recommended for controlled drug release. Dibutyl sebacate, diethyl phthalate, triacetin, triethyl citrate, and acetylated monoglyceride often give satisfactory results.

2. *The amount of the plasticizer.* Experiments should be performed to determine the most favorable proportion of plasticizer. Low levels of plasticizer may not overcome the latex sphere's resistance to deformation and result in incomplete or a discontinuous film. On the other hand, a high proportion of plasticizer may result in seed agglomeration, sticking, and poor fluidization problems caused by excessive softening of the polymer film. The best result generally is obtained with plasticizer concentration in the range of 15–30% based upon the polymer.

3. *Incorporation of plasticizer.* Plasticizer can be incorporated into the latex system during the preparation process which provides more consistent plasticization, more effective use of plasticizer, and a relatively nonseparable plasticized latex system. Plasticizer also can be added to the latex system under mild agitation. Agitation speed, mixing time, and separation of plasticizer during the coating process should be considered in the preparation of the plasticized latex system.

4. *The solids content of the latex system.* Generally, 8–20% solids content give the best results [112]. However, higher or lower solids content can be used to achieve a rapid buildup of film thickness or coating uniformity, respectively.

5. *Additive.* Water-soluble chemicals can be incorporated into the latex film to enhance its dissolution rate. On the other hand, the addition of hydrophobic powder such as talc, magnesium, stearate, or silica in a latex-coating system not only alters drug release, but also facilitates processing by reducing tackiness of the polymer film.

6. *Dual Latex/pseudolatex coating.* Most latice or pseudolatices are stabilized by high surface potential of deflocculated particles arising from ionic functional groups on the polymer or ionic surfactant or stabilizer. For example, the positive charge on Eudragit RS30D and RL30D pseudolatex particles arising from quaternary groups on the polymers and the negative charge on Aquacoat and Surelease pseudolatex particles originated from the anionic surfactants such as sodium lauryl sulfate and oleic acid are the major stabilizing factor. Also, the size of the latex sphere and size distribution are important factors which affect stability, rheological properties, and film properties. Small, monodispersed latex particles are required to have complete coalescence of the latex sphere. Generally, it is not recommended to use dual latex/pseudolatex coating systems because of the possible incompatibility of two latex/pseudolates systems, the different glass-transition temperatures of the polymers, and th different sizes of latex spheres. However, in a British patent, Eudragit E-30D was mixed with Aquacoat to prevent the coated granules sticking together and to

improve the dissolution-retarding effect [116]. It has been demonstrated that Eudragit RS pseudolatex can be mixed in any proportion with Eudragit RL pseudolatex. A wide range of release rates for theophylline could be obtained by changing the ratios of Eudragit RS pseudolatex and Eudragit RL pseudolatex. The enhancement of theophylline release caused by increasing the amount of Eudragit RL pseudolatex is due to its high permeability to water and theophylline [80].

7. *Overcoating.* During the curing or storage stage, the pellets coated with latex or pseudolatex may adhere to one another because of the softening and tackiness of the film. This could have a detrimental effect on the dissolution properties of film-coated products. Nevertheless, an overcoat that is water soluble can solve the problem of tackiness of latex film without changing the dissolution profile. Immediate mixing of latex-coated pellets with some separating agents such as talcum, magnesium stearate, and other diluents also can prevent the formation of clumps of pellets during storage.

C. Compression Coating and Embedment

Specially constructed tablet presses such as Drycota and Prescota are available for compressing a polymeric or sugar composition onto a drug-containing core. This technique has been utilized to create a polyvinyl alcohol diffusion barrier surrounding a core tablet containing various active ingredients as described by Conte et al. [117]. In vitro dissolution tests show that zero-order release kinetics of drug from compression-coated tablets can be achieved as long as the thermodynamic activity of the drug within the closure and the barrier characteristics are maintained constant. Salomon et al. [118] coated potassium chloride tablets with a thin layer of hydroxypropyl methylcellulose by a compression technique for delayed-release purposes. Such compression-coated tablets release potassium chloride at a constant rate. Enteric coating by a double-compression technique has been reported [119] using a mixture of triethanolamine cellulose acetate and lactose as coating materials.

Other variations of compression coatings such as inlaid tablets and layer tablets may have application in preparing a sustained-release tablet with an immediate-release and a separate slow-release portion. In general, the release rate from compression-coated tablets may be modified by core composition and characteristics, thickness of membrane layer, composition of membrane layer, and geometry of core tablet and final tablet. However, the expense of compression coating and layer tablet production, complicated mechanical operation, production problems such as multiple granulations, improper centration, capping, and limited compressible and permeable barrier materials limits its adoption as a popular technique to control drug release. The compression-embedding technique has received increasing attention to prepare controlled-release matrix tablets, and intensive research in this area is being conducted by pharmaceutical scientists. There are three different types of matrix tablets; i.e., hydrophilic matrices, plastic matrices, and fat-wax matrices, which can be differentiated by the matrix-building materials.

Hydrophilic Matrix Tablet

Utilization of a hydrophilic matrix as a means to control drug release was disclosed in U.S. Patent 3,065,143. Sodium carboxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, polyethylene oxide, polyvinyl pyrrolidone, polyvinyl acetate, carboxy polymethylene, alginic acid, gelatin, and natural gums can be used as matrix materials. The matrix may be tableted by direct compression of the blend of active ingredient(s) and certain hydrophilic carriers, or from a wet granulation containing the drug and hydrophilic matrix material(s). Several commercial patented hydrophilic matrix systems are currently in use, such as the Synchron Technology [120] and hydrodynamically balanced system [121]. The hydrophilic matrix requires water to activate the release mechanism and enjoys several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Upon immersion in water, the hydrophilic matrix quickly forms a gel layer around the tablet. Drug release is controlled by a gel diffusional barrier that is formed and/or tablet erosion. The effect of formulation and processing variables on drug-release behavior from compressed hydrophilic matrices has been studied by a number of investigators [122–134] and can be summarized as follows:

1. The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is particularly true for formulation of water-soluble drugs and excipients.
2. The amount of hydrophilic polymer in tablet formulations was reported to have a marked influence on the disintegration time and dissolution of the tablet. The disintegration time was extended as polymer content increased. The release rate of drug was decreased when the proportion of polymer was increased but differed quantitatively with different drugs and different matrix-building materials. Slower hydration polymers can be used at higher concentration level to accelerate gel formation or reserved for water-insoluble drug(s).
3. Generally, reduced particle size of the hydrophilic polymer ensures rapid hydration and gel formation, leading to a good controlled release. The impact of polymer particle size on the release rate is formulation dependent, but may be obscured in some cases. The particle size of a drug, within a normal size range, may not significantly influence th drug release from the matrix tablet. Extremes of drug particle size may affect release rate of the drug.
4. Viscosity characteristics of the polymers are of great importance in determining the final release properties of the matrix tablet. Generally, the drug-release rate is slower for a higher viscosity–grade polymer.
5. Commonly, water-soluble excipients in the matrix tablet can increase drug release. However, addition of water-soluble materials may achiev a slower rate by increasing viscosity of the gel through interaction with hydrophilic polymers or by competition with matrix material for water. When water-insoluble nonswellable excipient(s) or drug(s) is used in the matrix system stress cracks can occur upon immersion in water becaus of the combination of swelling and nonswelling comp n nts on the tablet surface.

6. For some hydrophilic matrix building materials, pH may affect the viscosity of th gel which forms on the tablet surface and its subsequent rate of hydration. Under acidic conditions, carboxypolymethylene and sodium carboxymethyl cellulose have little or no retarding effect on the drug-release rate. Gelatin forms gels of higher viscosity in acidic media and is more effective in retarding drug release as compared to a basic media.

7. No conclusions could be drawn as to the effect of compression force on drug-release behavior owing to the different properties of the various hydrophilic matrix materials. However, tablet size and shape can significantly influence drug-release kinetics.

Fat-Wax Matrix Tablet

The drug can be incorporated into fat-wax granulations by spray congealing in air [135–138], blend congealing in an aqueous media with or without the aid of surfactants [139–142], and spray-drying techniques [44]. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminuted for sustained-release granulations [143]. The mixture of active ingredients, waxy material(s), and filler(s) also can be converted into granules by compacting with a roller compactor, heating in a suitable mixer such as a fluidized-bed and steam-jacketed blender, or granulating with a solution of waxy material or other binders. Fat-wax granulations containing drug obtained from all of the above processes may be compressed to form tablet cores or directly compressed into a final tablet form with sustained-release properties.

The drug embedded into a melt of fats and waxes is released by leaching and/or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the gastrointestinal tract. Enteric materials such as cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylate copolymer, zein, and shellac may be used to prepare matrix tablets with somewhat a similar drug-release mechanism. In general, the primary constituents of a fat-wax matrix are fatty acids and/or fatty esters. Fatty acids are more soluble in an alkaline rather than an acidic medium. Fatty esters are more suscepitble to alkaline catalyzed hydrolysis than to acid catalyzed hydrolysis. The surface erosion of a fat-wax matrix depends upon the nature and percent of fat-wax and extenders in the matrix [136]. Other factors such as drug particle size and drug concentration affects release of the drug from the matrix system [141]. The addition of surfactants to the formulation can also influence both the drug-release rate and the proportion of total drug that can be incorporated into a matrix [137,142]. Polyethylene, ethylcellulose, and glyceryl esters of hydrogenated resins have been added to modify the drug-release pattern [135].

Plastic Matrix Tablets

Sustained-release tablets based upon an inert compressed plastic matrix were first introduced in 1960 and have been used extensively clinically [144]. Release is usually delayed because the dissolved drug has to diffuse through a capillary network between the compacted polymer particles. Commonly used plastic matrix materials are polyvinyl chloride, polyethylene, vinyl acetate/vinyl chloride copolymer, vinylidene chloride/acrylonitryle copolymer, acrylate/methyl methacrylate copolymer, ethyl cellulose,

cellulose acetate, and polystyren [145]. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic material(s) provided the plastic material can be comminuted or granulated to desired particle size to facilitate mixing with drug particle. In order to granulate for compression into tablets the embedding process may be accomplished by:

1. The solid drug and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agents in an organic solvent and then granulated.
2. The drug can be dissolved in the plastic by using an organic solvent and granulated upon evaporation of the solvent.
3. Using latex or pseudolatex as granulating fluid to granulate the drug and plastic masses.

Drug release from the inert plastic matrices was affected by varying formulation factors such as the matrix material, amount of drug incorporated in the matrix, drug solubility in the dissolution media and in the matrix, matrix additives, and the release media. Since the mechanism of controlling drug release in the plastic matrix is the pore structure of the matrix, any formulation factors affecting the release of a drug from the matrix may be a consequence of their primary effect on apparent porosities and tortuosities of the matrices. These release factors can be summarized as follows:

1. The release rate increases as the solubility of the drug increases, but there seems to be no direct relationship between the two variables.
2. The release rate increases as the drug concentration increases. An increase in release rate cannot be explained on the basis of increasing matrix porosity [146]. Rather it has been attributed to changes in matrix tortuosity with drug concentration [147] and to decreased diffusional resistance by shortening the length of the capillary joining any two drug particles [148].
3. It is possible to modify the release rate by inclusion of hydrophilic or hydrophobic additives to the matrix. The release of a sparingly soluble substance can be increased by the addition of physiologically inert but readily soluble material such as polyethylene glycol, sugars, electrolytes, and urea [146,149]. The decrease in the release rate on the addition of hydrophobic substance may be due to decreased wettability of the matrix [150].
4. The release rate from plastic matrix tablets could be decreased by exposure to acetone vapor without changing the release mechanism. The extent of the reduction was found to be dependent on the amount of acetone absorbed [147,151]. The tensile strength of the tablets increases by heating the polymer matrix above the glass-transition temperature. However, porosity also increases with a marked increase in the release rate [152,153].
5. The release rate increased as the particle size of the matrix material increased and as the particle size of the drug decreased.
6. Increasing compaction pressure up to the full consolidation point tends to decrease the pore formed among the polymer particles, resulting in a slower drug-release rate [154].

Microcapsules, microspheres, or coated pellets also can be compressed into tablets or embedded in a drug-containing matrix. Sustained-release tablets mad from individual coated particles may have very different release characteristics than the original coated particles depending upon whether or not the tablets disintegrate to expose the majority of the coated particles to the dissolution environment and whether the coated particles are damaged by the compression process [155]. Generally, nondisintegrating tablets made from ethyl cellulose microcapsules followed matrix-release kinetics are much slower than the uncompressed microcapsules. When compression force was sufficient to prevent breakup of the tablets, greater compression force had little effect on rate of dissolution [156–160]. Apparently, nondisintegrating tablets made from individual coated particles did not provide any advantages over matrix tablets but a more complicated manufacturing process. A dispersible tablet containing individual coated particles distributes the drug-containing coated particles in the gastric content to minimize the high local concentration of drug and to reduce the inter- and intrasubject variation linked to gastrointestinal transit time.

However, the sustained-release properties of the coated particles may be lost due to cracking of the membranes and rupture of the characteristic microcapsule tails. The amount of damage was found to be related to the compressibility and particle size of excipients in the tablet formula as well as to the compression pressure. Large particles led to greater damage as noted by increased dissolution rates of the disintegrating tablets [161]. It also has been found that a combination of microcrystalline cellulose and polyethylene glycol provides maximum protection from the damage of potassium chloride microcapsules by reducing interparticle friction [162]. Matrix particles have the advantage of being very rugged, less subject to dose dumping, and more resistant to compression damage than membrane systems. Little change in the dissolution rate of cellulose acetate butyrate microspheres containing succinyl sulfathiazole has been reported when tableting with microcrystalline cellulose and carboxymethyl starch under compression force between 35 and 350 MPa [163].

IV. SUSTAINED-RELEASE PRODUCTS THROUGH COATING

The preceding discussion has provided the framework for the design of sustained-release products. Application of these principles in the pharmaceutical industry has resulted in varying degrees of success in achieving consistent, nonvarying blood levels of drug from sustained-release dosage forms. It is instructive to examine some of these dosage forms more closely, and to analyze where and why they fail to provide sustained release and whether the failure can be detected in vivo or in vitro. Of course, the reader should keep in mind that these are "failures" only in a relative sense; some forms are very much superior to others, but all do provide some sort of sustained therapy beyond their nonsustained counterparts. Whether this sustained blood or tissue level results in a measurable improvement clinically is often debatable.

It would appear from the earlier sections of this chapter that one can employ the theoretical calculations on release-rate and dosage-form design with great precision to formulate a prolonged-action dosage form. In point of fact, although this has been done in a few studies, the vast

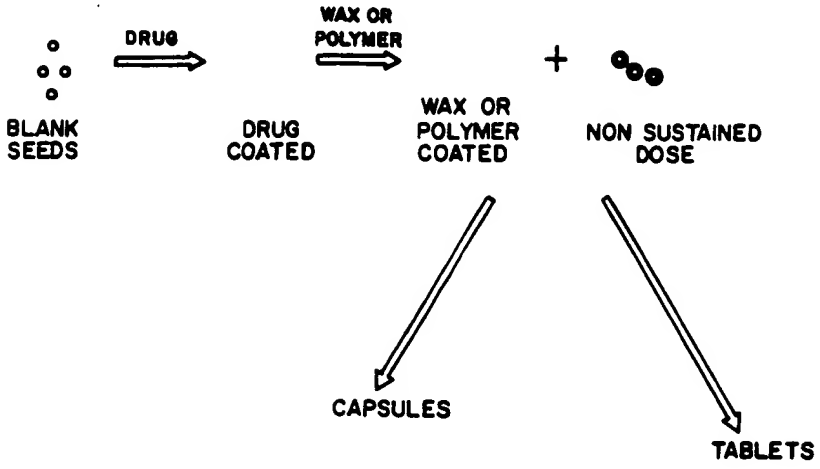
majority of published work has employed these principles and calculations as a working guidelin . The formulator obtains the d sired release-rate constant and size of tablet by suitable calculation and attempts to generate this release pattern by some sustained-release mechanism, such as coating. If the release rate of drug is dissimilar to the calculated value, the dosage form is appropriately modified. Since the ideal release pattern, resulting in a tissue drug concentration–time profile similar to that shown in Figure 1, is seldom obtained, the formulator will usually be satisfied with either a bell-shaped profile that has a broad, relatively flat plateau, or an extension of biological activity. This qualitative approach, which at times is very empirical, is clearly evident when one reads the literature dealing with prolonged-action dosage forms. Thus, unless the formulator has good control over the release mechanism, which is rarely the case, he or she will be working empirically or semiempirically in preparing the dosage form. Moreover, because of this lack of control over the release mechanism, a blood drug profile will usually result that shows simple prolongation rather than the invariant drug level of the sustained type.

In the following discussion, we have arbitrarily classified the approaches used in coating sustained-release products into various subdivisions. A good argument could be constructed that all of the following subdivisions are artificial, since all coated sustained-release dosage forms utilize dissolution and diffusion to varying degrees. However, the dosage forms m ntioned in each section usually appear to have one major mode of providing sustained action. These modes can derive from the way the material is produced, as in the case of microcapsules and bead polymerization, or from the way the body handles the dosage form, as in the case of soluble coated granules or impermeable films coated in a tablet. The division has been created solely for the purpose of organizing the literature in the area and should not be viewed as being rigid or exclusive.

At the end of some of the subdivisions, the reader will find a section entitled case study. These sections are intended to provide sufficient experimental detail to allow the novice formulator to initiate preparation of a prolonged-action dosage form. We will thus examine selected published reports in more detail, providing as much of the experimental methods employed as is practical. In addition, when available, the appropriate equations to describe the release of drug from the dosage form and the type of in vitro and in vivo profile generated will be noted.

A. Sustained Release Utilizing Dissolution

Dissolution methods in sustained release generally refer to coating the individual particles, or granules, of the drug with varying thicknesses of coating material so that dissolution of the coat, resulting in release of the drug contained within, occurs over a long time span owing to the thickness differences of the coats. These coated particles are then either compressed directly into tablets (e.g., Spacetabs), or they can be placed in capsules (e.g., the Spansule or Plateau Cap dosage forms), as shown in Scheme 11. Alternatively, the dissolution may be that of an ext rior tabl t coating where a portion of th drug is placed in th tablet coat and dissolves rapidly to provid nough drug to quickly reach therapeutic levels, whereas the sustained-release interi r of the tablet utiliz s som other m thod, to b discuss d subsequently, t provide controlled, long-term release of



Scheme 11

medicament. Exterior tablet coats may also have differentially soluble constituents that dissolve and provide an outer shell to maintain diffusion path lengths for the drugs contained in the shell. This form of sustained release is particularly useful for relatively insoluble drugs because it keeps the dose from disintegrating and being spread out over the gastrointestinal tract, thus providing some regulation of the dissolution medium and area for control in maintaining slow release of drug.

Pulsed Dosing

Included in the pulsed dosing category are slowly dissolving coatings such as the various combinations of carbohydrate sugars and cellulose-based coatings as well as polyethyleneglycol bases, polymeric bases, and wax-based coatings. Colbert [164] and Johnson [165] provided a particularly complete cross section of patents issued since 1960 based on these digestible bases. These coating materials are used in preparing sustained-release dosage forms that follow the approach of various thickness coated granules or seeds combined with uncoated granules which are dispensed in capsule or compressed tablet form. Examples are the Spansule [166–175] and Spacetab [176–180] formulations. These coatings vary in thickness and when they cover a drug granule their digestion by fluids in the gastrointestinal tract results in abrupt release of the medicament at selected time intervals to provide pulsed dosing for periods up to approximately 12 h.

With digestible coating materials, the important factors a formulator must take into account are the dissolution rate of the coating material, the thickness of the coat, and the changed are for disintegration and dissolution that the increased thickness provides [3–5,10,18,181,182]. As th drug-coated granules traverse the gastrointestinal tract, the coating is slowly solubilized by the gastrointestinal fluids. Since the granules hav varying thickness coats, one anticipates a staggered release of drug. Therefore, by combining a large number of mixes of different thickness coated granules, a horizontal, or v ry nearly so, blood drug concentration

versus time curv for extended periods of time should result. In practice, it is often difficult to combin a large numb r of granules having many different thicknesses of coating, so that the more common approach is to employ one-quarter of the granules in uncoated form, thus providing for immediate release and rapid attainment of therapeutic blood levels of drug, with the remaining three-quarters of the granules being split into three groups of varying coating thicknesses to provide a sustaining effect, through pulsed dosing, over the desired time period. Although the approach of one-quarter uncoated, three-quarters coated is very common, other combinations, such as one-third coated, two-thirds uncoated, have also been employed. The ratio is determined by properties of the coated granules; that is, dissolution rate and derived drug properties such as the elimination rate constant.

CAPSULES. Since the introduction of the Spansule sustained-release dosage form in the early 1950s, there have been numerous studies on the release of active drugs from this type of preparation [172,173,183–198], and also on the clinical effectiveness of these preparations in maintaining therapeutic activity over extended time periods [166–171,174]. Examples of the types of drug formulated as coated granules include antihistamines [166,167], belladonna alkaloids [168,171], phenothiazines [173,174,185,187], combinations of the above [169], antihypertensives [45], cardiac muscle dilators [199–201], anorexigenic agents [175,184,187,192,193], steroid anti-inflammatories [183], and nonsteroidal anti-inflammatories such as aspirin [191].

There are several ways to prepare drug-coated beads or granules. A common procedure is to coat nonpareil seeds with the drug and follow this with either a slowly dissolving wax or polymer coat of varying thickness. Conventional pan-coating or air-suspension coating techniques can be employed for this purpose. Types of coating materials and properties will be discussed later in this chapter. Coatings such as these can also be accomplished through microencapsulation, to be discussed shortly, wherein the drug solution or crystal is encapsulated with a coating substance. The selection of coating material dictates whether pulsed or sustained drug release occurs.

An illustration of this approach is the series of papers by Rosen et al. [189,190] in which they describe the release of ^{14}C-labeled Dextroamphetamine sulfate and ^{14}C-labeled amobarbital from both non-sustained- and sustained-release dosage forms employing wax-coated granules. As can be seen in Figure 3, the amount of drug released in each time period is progressively less as the percentage of wax-fat in the coating increases. This is the expected behavior, and indicates that sustained release can be varied quite readily by changing the makeup of the coating material for the drug granules. Other studies [185,191] along these same lines have indicated that such behavior of coated granules is the general rule. Not in Figure 3 that continuous release of drug occurs. This is because a spectrum of granule size was employed in the study. The dashed line in Figure 3 indicates the release pattern when only a few granule sizes are combined.

The coated granules or seeds can be placed into a capsule for administration to the patient. Actual photographs of the in vivo disintegration and dispersal of coated sustained-release granules in a capsule were provided in a series of papers by Feinblatt et al. [200,201]. Using

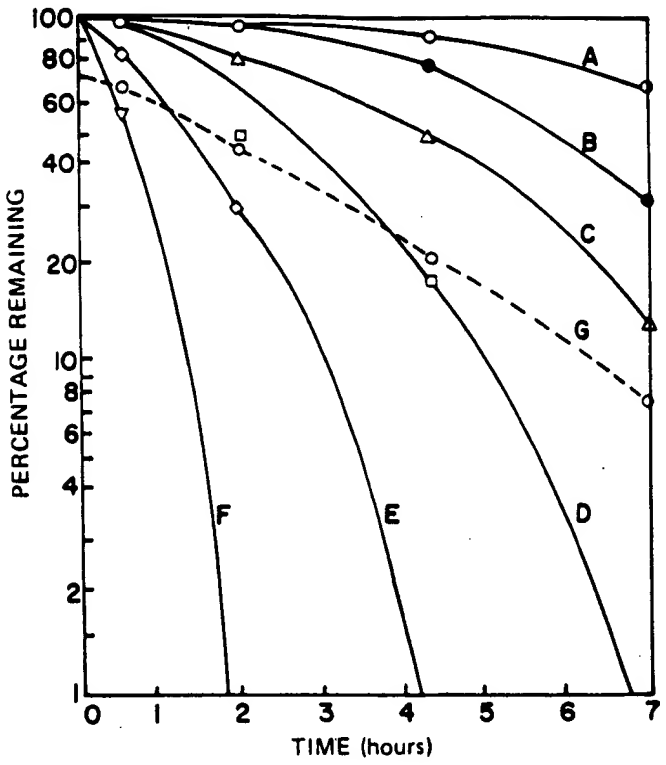


Figure 3 In vitro release pattern of dextroamphetamine sulfate pellets pan coated with various amounts of wax-fat coating. (A) 17% coating, (B) 15% coating, (C) 13% coating, (D) 11% coating, (E) 9% coating, (F) 7% coating, and (G) selected blend of uncoated pellets and coated pellets. (From Ref. 189, used with permission.)

roentgenography, the authors showed that after 10–12 h the coated granules in a sustained-release capsule were well dispersed in the gastrointestinal tract and the active ingredient was completely dissolved.

In a different study concerned with in vitro measurement of drug release from sustained-release coated granules in a capsule, Royal [192] described a modification of the *United States Pharmacopeia* (USP) tablet disintegration apparatus that allowed him to follow the release of drug from capsule dosage forms. Further modifications [193] allowed him to test different brands of capsules containing a wide range of granule sizes, and thus be able to compare the brands as to their efficiency in maintaining continuous release of medicament for extended time periods. Souder and Ellenbogen [175] described a method for "splitting" (separating) sustained-release coated granules to ensure an even mix of large and small granules and to prevent the stratification of such mixes that often occurs when pooling granules for analysis. They then measured timed rel ase of drug in a manner differing som what from the approach us d by Royal. Th results, however, w re th sam , and indicated that the blending of larger and smaller coated granules, presumably due to thickness of the sustained-release coating, was effective in maintaining the characteristics of sustained drug release. Th r ar several approaches that can b employed for

dissolution testing of coated pellets, and most investigators employ m difications of the rotating vial techniques, such as is described in the *National Formulary* (NF) XIII, or modification of the dissolution test presented in USP XIX.

In clinical evaluations of capsule pulsed dose, prolonged-action dosage form, and sustained-release products, the objectives of the experimental techniques change from that of ensuring that drug release is indeed occurring gradually over a long time to that of (1) showing that the sustained-release dosage form adequately maintains therapeutic blood or tissue levels for extended times [172,173,183,185–188,191], (2) provides relief to the patient over a long period [166–169,171,174], and (3) perhaps reduces the incidence of side effects due to the "peak" effects of non-sustained-release dosing [166,167,169]. Of course, many of the earlier studies were conducted before development of the sophisticated methods now employed in gathering and interpreting blood or tissue drug level data [166,167,169, 171,174], and indeed many such studies were rather qualitative in their assessment of prolonged-action dosage forms. As a result of this lack of sophistication, the focus was either on monitoring some biological respons or on urinary receovery of active drug or its metabolites. For example, the reports of Heimlich et al. [172,173] on sustained-release phenylpropanolamine and trimeprazine and of Sugerman and Rosen [188] on sustain d-release chlorpromazine present very detailed and thorough urinary analyses of drug content and provide, within the limitations set forth by the authors, a very good analysis of sustained-release characteristics and their worth with respect to administration of these drugs. While results of urinary drug analysis alone can give quantitative information on sustained-release characteristics, it has been pointed out [202] that there are dangers in this approach and comparisons of blood and urine data do not always coincide. When possible, both blood and urine samples should be collected and analyzed.

In the early 1960s, the first really good effort at measuring and analyzing drug levels in the blood began to appear in the literature [183–186]. One of the earliest of these is the study by Wagner et al. [183] on the sustained action of prednisolone in dogs and humans and the comparability of these data to in vitro findings. The work by Rosen and Swintosky [187,189,190] contributed to this field by employing radioactive-labeled drug.

Hollister [186], in a report on sustained-release meprobamate products, presented both urine and blood drug level data and pointed out how they reinforce the interpretation based solely on one or the other.

Of course the nature of the disease state itself can be a major reason for publishing more qualitative results, as was one in some of the earlier work. Those studies measuring relief of symptoms due to sustained-release antihistamines [166,167] have few measurable effects that are easily quantitated, whereas other reports in the area, such as those dealing with ulcer patients and relief of pain, can at least quantitate volume and acidity of gastric acid and digestive juic s [168]. The literature is speckled with data that show a sustained effect is operative, but give no indication as t how well it compares to multiple dosing of ordinary tablets.

The qu stion of th bioavailability of sustained-release dosage forms as compared to conv ntional syst ms is an important issu . For most drugs placed in a sustain d-release system, the bioavailability is less than in c nventional dosage forms. There are the occasional drugs that are unstable

in gastrointestinal fluid or have absorption problems [31] which become stabilized or show improved absorption when placed in a sustained-release system. A typical example of reduced bioavailability is the study by Henning and Nybert [203] on quinidine, in which the rapidly dissolving tablet was shown to have greater bioavailability than either quinidine Durules or Longacor. Compared to the rapidly dissolving tablet, the Durules had a bioavailability of 76% and the Longacor 54%.

TABLETS. With the tablet dosage form the concern for the thickness and area of granular coating remains, the distinguishing feature of this dosage form being that of tablet disintegration as contrasted to gelatin capsule dissolution. An added problem here may be the influence of excipients used to produce a compressed tablet in the disintegration/dissolution process. Of course, when no fillers or excipients are used, the coated granules alone are compressed and can fuse together, resulting in altered dissolution patterns [18], depending on the properties of the coating material. The role of excipients on the dissolution pattern of compressed coated granules has not been investigated extensively. One would not expect substantial effects on the dissolution process of the individual seeds or granules, but perhaps there would be an influence on fracture or fusing of seeds. Reports using other sustaining mechanisms show, as one would expect, that in compression some of the coated particles are fractured. Green [204], for example, found that in microencapsulated sustained-release aspirin which was subsequently tableted, a small amount of aspirin was immediately released, suggestive of fractured coats. This need not be a problem, since the degree of fracture and immediate release is frequently small and can usually be incorporated into that portion of the dosage form that provides for immediate blood drug levels. Other studies have shown that the dissolution pattern was very much influenced by tablet hardness, so that compression force would be important. These findings were with specific formuations, but they suggest that these variables must be considered.

Because the dissolution patterns of sustained-release coated granules are essentially the same whether the granules are filled into a capsule or compressed with excipients into a tablet, the dissolution studies described earlier are applicable here provided extensive fusing of the granules does not occur in the tableting process.

Here, as in the case of capsules, there has been a wide range of drugs formulated as sustained-release coated granules and compressed into tablets. Antispasmodic-sedative combinations have been investigated [176], as have phenothiazines [172–180], anticholinesterase agents, and aspirin [205,206].

Steigmann and coworkers [176] described the clinical evaluation of Belladenal Spacetabs, a combination of the natural levoratory alkaloids of belladonna and phenobarbital, in patients with peptic ulcer and other gastrointestinal disorders. They measured gastric secretion and bowel motility and found that, for the most part, the results with the Spacetabs formulation were as good or better than those obtained with conventional nonsustained forms, and the convenience to the patient of once or twice a day dosing was recognized.

The treatment of myasthenia gravis with neostigmine bromide formulated as Mestinon Bromide Timespan was examined by Magee and Westerberg

[205]. The need for sustained releas is particularly acute here, since with treatment via non-sustained-release dosage forms, the patient generally is very weak upon arising in the morning and remains in this state until the morning tablet dose can be absorbed. A means of maintaining patient strength and comfort throughout the hours of sleep was needed. The results of their study show that the value of this sustained-release dosage form is greatest when taken at bedtime, at times even allowing the patient to arise with sufficient strength to dress before taking morning medication. Results of daytime use were variable, and absorption appeared to be less than optimal in comparison with non-sustained-release tablets.

Probably the largest body of clinical data has been compiled for the phenothiazine tranquilizer thioridazine. Mellinger [177], in an early evaluation of thioridazine formulated as Mellaril Spacetabs, examined serum concentrations following administration of the drug as a liquid concentrate, as tablets crushed in a mortar, as intact tablets, and as the Spacetab sustained-release tablet. He found that the drug persists in the blood for long periods from all the dosage forms studied, and attributed its slow excretion to possible slow metabolism. There were no striking advantages to the sustained-release formulation over that of conventional tablets. This last finding has been reiterated by other workers [178], and as of this time, the Spacetab formulation of thioridazine is not being marketed.

The clinical evaluation and comparison of sustained-release and non-sustained-release aspirin tablets was reported by Cass and Frederik [206, 207]. They measured the duration of analgesic relief obtained via a series of different dosage regimens in patients suffering from a variety of coronic illnesses. In all cases, the sustained release form provided longer and more predictable analgesic relief than any of the other non-sustained-release tablets tested.

Case Study of Slowly Soluble Wax Coating on Nonpareil Seeds [189]. *Prolonged action mechanism.* Pulsed dosing in repeat action fashion. Drug-containing nonpareil seeds were coated with various thicknesses of digestible waxes which were intended to release drug at various times after dosing.

Type and method of coating. A kilogram of medicated non-sustained-release pellets was prepared in a 12-in coating pan. The pellets were composed of 31.2 gm of dextroamphetamine sulfate; 58.8 gm of a 1:1 mixture of starch, USP, and powdered sucrose, USP; and 90 gm of U.S. No. 16 to 20-mesh sugar pellets. The nonpareil seeds were placed in a conventional coating pan and wetted with a water/alcohol/gelatin mixture consisting of gelatin 10% w/v, hydrochloric acid 0.5% v/v, and water 30% v/v, and alcohol 70% v/v (90% ethanol, 10% methanol). When the mixture became tacky the drug diluent was added to the rotating seeds. After a short period of drying, one-fourth of the seeds were removed (these represented the uncoated portion). The remaining seeds were then coated to varying thicknesses with a wax formula consisting of glyceryl monostearate 11% w/w, glyceryl distearate, 16% w/w, white wax 3% w/w, in carbon tetrachloride 70% w/w. Six different groups of pellets with approximately 7, 9, 11, 13, 15, and 17% of wax coating were initially prepared and, through trial and error, a final blend consisting of 25% non-coated pellets, 55% of the 11% wax-coated seeds, and 20% of the 9% wax-coated seeds gave a satisfactory in vitro release pattern. Each group of

Table 8 Blend and Desired in Vitro Release Patterns, [^{14}C]Dextroamphetamine Sulfate

	% In vitro release at time interval (h)			
	0.5	2	4.5	7
Blend	34	56	79	92
Desired[a]	39	62	80	90

[a]Average in vitro pattern of 15 commercial lots of sustained release dextroamphetamine [190].

pellets was screened through U.S. No. 12 onto U.S. No. 25 standard mesh sieves to remove lumps and fines.

In vitro test. In vitro dissolution tests in artificial gastrointestinal fluids were conducted according to the method of Souder and Ellenbogen [50]. The dissolution pattern for all six coated seeds is shown in Figure 3, and the results on the blend in Table 8. A satisfactory prolongation is obtained.

In vivo release. The in vivo release study was conducted in humans and employed the following dosage regimens;

1. 15-mg sustained-release dosage form
2. 15-mg nonsustained dosage form
3. 5-mg nonsustained dosage form
4. 5-mg sustained-release dosage form given at intervals of 0, 4, and 8 h

This particular plan was chosen to determine performance criteria of

1. Whether the sustained-release formulation provided a prompt initial dose
2. Whether it was similar to 3 times daily drug administration
3. Whether it was dissimilar to an equivalent nonsustained dose
4. Whether equal doses in different dosage forms were equally effective in making drug available for absorption
5. Whether there was any significant variability among subjects receiving the various regimens

The study was conducted in a crossover sequence, as shown in Table 9.

Blood and urine samples were collected at various times postdosing, and the results are shown in Figures 4 and 5. The cumulative urinary excretion data for human subjects is shown in Table 10. From the table the following conclusions were drawn:

1. In the first 3 h following administration of the drug, the sustained-release, 3 times daily regimen, and the 5-mg single dose were

Table 9 Human Study Plan of Various Dosage Regimens

Subject	Initial[a]	1 Week later
1	A	B
2	B	C
3	C	D
4	D	A
5	A	C
6	B	D
7	C	A
8	D	B
9	A	D
10	B	A
11	C	B
12	D	C
13	A	D
14	B	C
15	C	B
16	D	A

[a]A, 15-mg sustained release dosage form given at 0 h; B, 15-mg non-sustained-release dosage form given at 0 h; C, 5-mg non-sustained-release dosage form given at 0 h; D, 5-mg non-sustained-release dosage form given tid, at 0, 4, and 8 h.
Source: From Ref. 189, used with permission.

similar. Thus, the sustained-release formulation did provide a prompt initial dose.

2. The plasma and urine plots for the sustained and 3 times daily regimen were similar, whereas the sustained and 15-mg plain capsul were dissimilar.
3. The sustained-release dosage form made as much drug available as the other two 15-mg regimens.
4. The variation in plasma and urine data is not greater with the sustained-release dosage form than with the 3 times daily regimen.

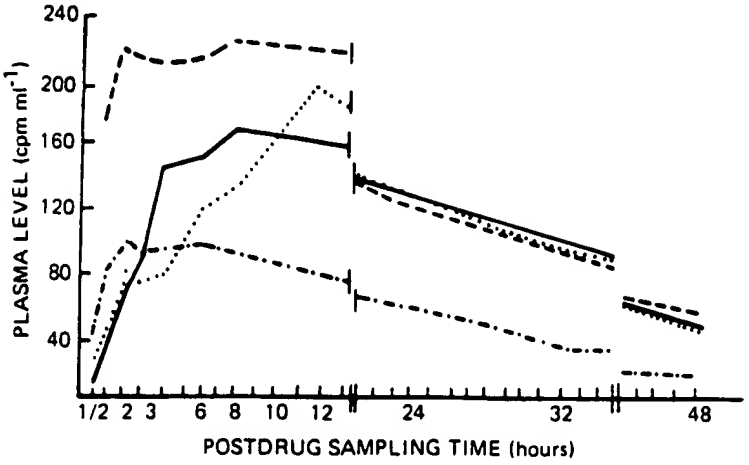


Figure 4 Adjusted average human plasma levels. Each line represents eight subjects per regimen in a balanced incomplete block crossover design. ———, 15-mg dextroamphetamine sulfate sustained-release dosage form; ·····, 5-mg dextroamphetamine sulfate capsule, tid; – – – –, 15-mg dextroamphetamine sulfate capsule; –·–·–, 5-mg dextroamphetamine sulfate capsule. (From Ref. 189, used with permission.)

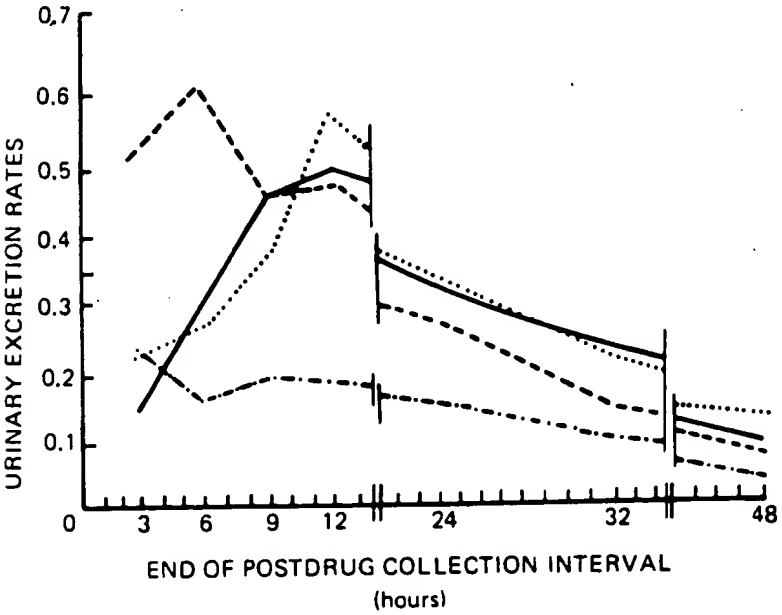


Figure 5 Adjusted average human urinary excretion rates. Radioactive counts are expressed as average milligrams of dextroamphetamine sulfate per collection interval divided by the number of hours in each interval. ———, 15-mg dextroamphetamine sulfate sustained-release dosage form; ·····, 5-mg dextroamphetamine sulfate capsule, tid; – – – –, 15-mg dextroamphetamine sulfate capsule; –·–·–, 5-mg dextroamphetamine sulfate capsule. (From Ref. 189, used with permission.)

Table 10 Adjusted Average[a] Urine Recoveries in Humans, mg of Dextroamphetamine Sulfate Equivalent

Dosage form	Collection interval (h)		
	0–12	0–24	0–48
5-mg capsule	2.18	3.90	4.89
15-mg sustained-release capsule	4.30[b]	8.24[b]	11.78[b]
5-mg capsule, 3 times each day	4.32	8.48	12.30
15-mg capsule	6.14	9.31	11.86

[a]Each figure is the average for eight humans.

[b]No figure included in a brace is significantly different from any other figure included in that brace ($p < 0.05$).

Source: From Ref. 189, used with permission.

Sustained Dosing

Although the principal factors controlling drug release are very similar in this case to those noted in the previous section, they do differ in at least one important aspect; that is, the drug is made available in a continuous rather than a pulsed fashion. The continuous release of drug is a result of the drug being impregnated in a slowly dissolving film; as dissolution occurs, drug becomes available [10,18,208–210]. This type of coating is very similar to the embedding of the drug in an insoluble matrix, which will be described later in this chapter. The difference lies in the fact that these products are microencapsulations of drug particles or granules, whereas the matrix tablets are formulated in a different manner.

MICROENCAPSULATION. Tanaka and coworkers [95] investigated the effects of formalin treatment on the hardness of gelatin microcapsules of sulfanilamide and riboflavin. As can be seen in Tables 11A and 11B, the treatment of gelatin micropellets containing sulfanilamide by immersion in 10% formalin/isopropanol for 24 h results in a 10-fold increase in time to release 100% of the drug. These results were mirrored when sulfanilamide and riboflavin micropellets were administered to dogs and blood levels of

Table 11A Dosages and Contents of SA and RF Micropellets[a]

Sample	Dosage and contents
1	Gelatin micropellet containing 33.2% SA
3	Micropellet, treated for 24 h, and containing 10.0% SA

[a]SA and RF refer to sulfanilamide and riboflavin, respectively.

Source: Reproduced with permission of the copyright owner.

Table 11B Percentage of Accumulative SA Recovered in the in Vitro Dissolution Test[a]

Sample 1		Sample 2	
Time	%	Time	%
5 min	32.9	5 min	5.9
10 min	59.5	10 min	9.9
15 min	76.5	20 min	30.7
35 min	80.0	30 min	39.6
1 h	89.6	45 min	53.4
2 h	99.5	1 h	61.5
3 h	99.7	2 h	82.0
		3 h	86.0
		5 h	91.6
		7 h	94.1
		23 h	98.2
		30 h	99.6

[a]SA and RF refer to sulfanilamide and riboflavin, respectively.
Source: Reproduced with permission of the copyright owner.

the drugs versus time were measured. Figures 6 and 7 show that, indeed, sustained blood levels of sulfanilamide and riboflavin were obtained when the micropellets were hardened. Nixon et al. [211,213] studied gelatin coacervate microcapsules of various sulfa drugs and the effect of various coacervating agents on in vitro release of drug. They found that hardened microcapsules gave a more prolonged release of drug in both acid and alkaline pepsin medium. Temperature and pH effects were also investigated, and from the data it was concluded that dissolution was the controlling step rather than diffusion of drug through a microcapsular wall.

The development of the complex form of coacervation as a tool for coating pharmaceuticals was developed by Phares and Sperandio [214]. The technique was further investigated and developed by Luzzi and Gerraughty [217,219] and by Madan et al. [215,216]. They examined the effects of varying starting pH, starting temperature, ratio of solid to encapsulating materials, quantity of denaturant, and final pH. Their results indicate that manipulation of all these variables affects some degree of change in the microcapsules and the resulting drug-release rate. When the drug to be encapsulated by the gelatin/acacia system was a waxy solid, such as stearyl alcohol, the coacervation procedure had to be modified because microscopic examination showed that, in the case of drug particles smaller

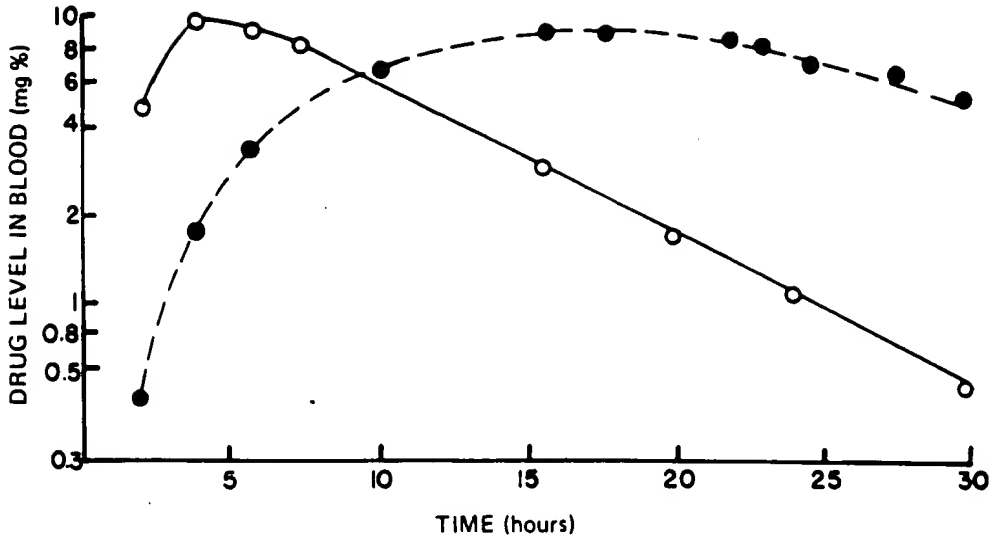


Figure 6 Logarithm of SA levels in blood against time after administration of SA gelatin micropellets to dogs. (○) Unitreated micropellets, (●) micropellets treated with formalin/isopropanol for 24 h. (From Ref. 213, used with permission.)

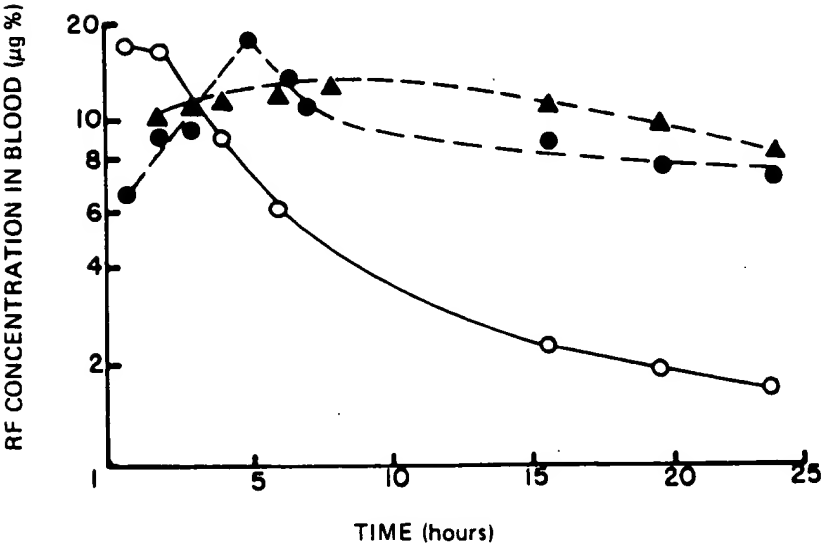


Figure 7 Logarithm of RF concentration in blood after administration of RF solution and its gelatin micropellets to dogs. (○) RF solution, ( ) untreated micropellets, (▲) micropellets treated with formalin/isopropanol for 24 h. (From Ref. 213, used with permission.)

than 250 μm, encapsulation was accomplished by several droplets aggregating and coalescing around the particles rather than by a single droplet as was the usual case. With drug particles larger than 250 μm, they suggested that encapsulation was the result of a direct interaction of gelatin with acacia on the surface of the particles. Scanning electron micrographs lend credence to their suggestion. Merkle and Speiser [218] prepared cellulose acetate phthalate coacervate microcapsules and evaluated them with respect to optimum coacervation and encapsulation conditions. Their findings indicate that while the amount of drug encapsulated had no significant effect on the particle size distribution of the microcapsules, it did influence the release rate. The suggested mechanism for this system is drug diffusion through the shells. When the shells are plasticized in a manner similar to that described earlier, the release rate control is altered from drug diffusion through the shells to dissolution of drug in the microcapsules.

More recently, Birrenbach and Speiser [220] employed polymerized micelles to produce very small particles, termed nanocapsules, to be distinguished from microcapsules. Although this approach is suggested for colloidal solutions to administer antigenic material, it has potential for parenteral drug delivery.

Nylon microcapsules have been examined by McGinity et al. [221], who described an improved method for making them, and by Luzzi et al., who evaluated the prolonged release properties of nylon microcapsules that had been either spray dried or vacuum dried. Both methods of drying produced a large reduction in the dissolution rates of the microcapsules, but since the spray-dried material was free flowing as compared with the vacuum-dried material, the authors felt that spray drying would result in more uniformity and reproducibility of release rates. On the other hand, increased release rates can be obtained by incorporating sucrose into the nylon microcapsules [18]. Interestingly, and perhaps not surprisingly, Luzzi et al. found when compressing these microcapsulated drugs into tablets that the release rate was inversely proportional to the tablet hardness.

Bead polymerization as a technique for preparing sustained-release dosage forms was described by Khanna et al. [222] and further evaluated by Khanna and Speiser [223]. This technique results in drug being embedded in the coating so that its release characteristics are similar to those to be described in the section on the plastic tablet below. By varying the concentration of the α-methacrylic acid content of the polymer solution, the coating can be made to release drug over a wide range of pH values and the release is prolonged for 12–15 h. By combining mixtures of beads with various concentrations of α-methacrylic acid, the correct sustained-release pattern can be made. Seager and Baker [224] described a somewhat different system for making microencapsulated particles in the subsieve size range. These resulted in drug being embedded in an inner core, whereas the outer core was a shellac coating. The release pattern showed good sustained-release properties.

Si-Nang et al. examined the diffusion rate of encapsulated drug as a function of microcapsule size. The influence of the coating on diffusion and the determination of the coating thickness were presented in terms of complex mathematical equations. The equations used were of a general nature and allow a quick estimation of the coating thickness, and thus can be useful in modifying the microencapsulation procedure to attain desired release capabilities.

Crosswell and Becker [225] reported a bead polymerization technique for producing sulfaethylthiadiazole and acetaminophen microencapsulations.

When polystyrene beads were produced in the presence of drug solution, no sustained release was evident; whereas if the beads were produced without drug present and allowed to expand via exposure to n-pentane and subsequent boiling in water, and then the drug solution was allowed to seep into the deep channels produced in the expanded polystyrene beads, the release pattern exhibited good sustaining properties.

The extensive use of polymer-drug interactions to produce sustained-release dosage forms was promoted by Willis and Banker [226]. The drug was made to interact with a cross-linked copolymer such as 1,12-dihydroxy-octadecone hemiester of poly(methylvinylether/maleic anhydride) and the salt that was formed as a result of this exhibited good sustained-release properties upon dialysis testing in artificial gastric and intestinal fluids of tablets and granules fashioned from the polymer-drug salt entities.

Banker and various coworkers [227–231] further studied molecular scale drug entrapment as a means of producing sustained-release dosage forms. Although the technique employed appears to be similar to bead polymerization, it is not clear whether each drug particle was coated (entrapped) within the polymer or whether the drug was actually chemically bonded to the polymer. For purposes of this discussion, the results are similar to those obtained via bead polymerization processes, so they are included here. The authors prepared and tested cationic drugs such as methapyrilene hydrochloride, chlorpromazine hydrochloride, atropine sulfate, etc., for their amenability to the entrapment procedures. The subsequent increases in sustained-release properties were tested and reported.

Further exploration revealed that additives such as organic acids could greatly facilitate drug entrapment by increasing the degree of interaction between the drug and the polymer, and could provide more control over the sustained-release characteristics. Other variables, such as flocculation pH, rate of agitation, use of different polymers, etc., can exert significant effects on sustained-release properties. Some of the important variables and their influences are described in Table 12.

Anionic drugs, such as sodium phenobarbital, sodium salicylate, chloral hydrate, etc., were also entrapped via coagulated (gelled) polymer emulsion systems. These polymer-drug products were tested in a manner similar to that employed for the cationic drugs and the increase in and reproducibility of the sustained-release products was noted. The authors make special mention of the fact that their procedures result in a highly uniform distribution of drug throughout the polymeric system and no drug segregation, with resultant variability in blood levels of drug after dosing, was evident upon scale-up processing and blending for incorporation into sustained-release dosage forms.

All the procedures mentioned thus far in this section are at least loosely related via their production of microencapsulated drug particles that employ slowly soluble films or coatings as the encapsulating material. A good portion of the literature in this area is experimental, usually resulting in statements that reflect how well these methods might be for actually producing commercial sustained-release products. As was mentioned earlier, very few products, aside from aspirin, have been actually formulated from these microencapsulated particles, and thus ther is a scarcity of clinical evaluations in the literature. In in vitro evaluation of sustained-release systems, one would like to have linearity in drug release versus tim up to 60–70% or more of drug content. How ver, it is

Table 12 (Continued)

Variable studied	Effect on entrapment	Ref.
	drug. This suggests mixing gel particle sizes to get a particular release pattern.	
Uniformity of distribution of amine drug in solid dispersions	Excellent reproducibility of drug content throughout the entire entrapment product as demonstrated in both flocculated (high drug levels) and deflocculated (low drug levels) systems. Dry blending was inferior to molecular scale drug entrapment in distributing small quantities of drug uniformly.	231

common to see studies showing linearity in the sustained effect for only 30–40% of the system. The study by Nixon and Walker [211] using gelation coacervate showed linearity up to 60% release.

Of the clinical evaluations reported, microencapsulated aspirin has received the lion's share of attention. Bell et al. [232] pointed out the need to monitor blood levels of both acetylsalicylic acid (ASA) and its metabolite, salicylic acid (SA). The need for this is obvious because ASA is reportedly far more potent as an analgesic than SA, so that modification of sustained-release products to provide more ASA and protect it from metabolism to SA become very important. The Bell study compared sustained-release aspirin versus regular aspirin administered as a single dose and in divided doses and analyzed the blood levels of ASA provided by each dosage form or regimen. This resulted in statements to the effect that sustained-release aspirin gave greater analgesic effects than regular aspirin because the ASA blood level remains higher for longer periods of time. When total salicylate blood levels are measured all salicylates presumably producing and contributing to the anti-inflammatory effect of aspirin, the sustained-release product still gave release rates that were too small for sustained-release aspirin. Optimum levels were achieved with about 3% of the drug in the encapsulated material.

Green [80] investigated sustained-release aspirin tablets formulated from microencapsulated particles and found the blood level curves of salicylate to be virtually flat with repeated dosing as opposed to a sawtooth effect exhibited with repeated dosing of regular aspirin. No conclusion was drawn from this observation, but the influence is that a flat blood level curve represents better control over the therapeutic regimen.

Rotstein et al. [233] examined sustained-release aspirin for use in the management of rheumatoid arthritis and osteoarthritis. In short-term double-blind crossover studies, the doses employed were large enough that the patients received relief from both regular and sustained-release aspirin and observabl differ nces between the two were obscured. However, in long-term usage studies, all the patients who had been on any type of previous salicylate therapy preferred the sustained-release aspirin.

formulation because it reduced the frequency of dosage and supplied more medication during the night hours, thus relieving the morning aches and pains of arthritis. In both studies the incidence of side effects was significantly lower with sustained-release therapy. These clinical studies have thus established that microencapsulation of aspirin formulated into sustained-release dosage forms is an attractive and effective alternative to nonsustained dosage forms.

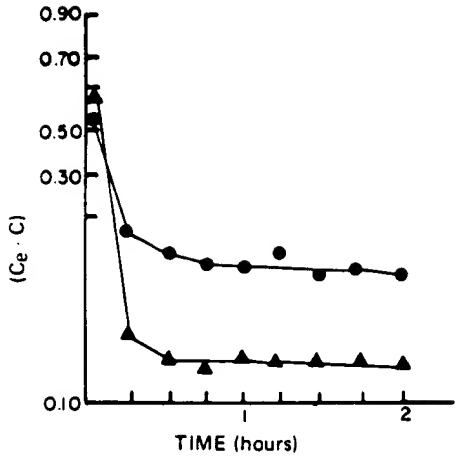
IMPREGNATION. There are two general methods of preparing drug-impregnated particles with wax: (1) congealing and, (2) aqueous dispersion. In the congealing method, the drug is admixed with the wax material and either screened or spray congealed. The aqueous dispersion approach is simply spraying or placing the drug-wax mixture in water and collecting the resulting particles.

In a series of papers by Becker and associates [225,234–239], the formulation and release characteristics of wax impregnations of sulfaethylthiadiazole were thoroughly investigated. The authors looked at dispersant concentration, effects of surfactant addition, effects of different waxes and modifiers, etc., as to their effect on release rate and proportion of total drug constituting the prolonged-release fraction. As might be expected, the size of the microcapsules produced and the physical properties of the various wax coating materials had profound effects on the release patterns reported. When the spray-congealed formulations of wax and sulfaethylthiadiazole were compressed into tablets the release mechanism appeared to be due to erosion, solubilization, and leaching of the drug from the tablet. No one model could describe the release pattern over the 48-h period of the study. It has been reported, in general terms, that the aqueous dispersion method gives higher release rates for all waxes tested, presumably due to increased area and perhaps the physical entrapment of water. Further, with aspirin as the test drug, the dissolution rate increases in the order stearic acid > spermaceti > hydrogenated cottonseed oil.

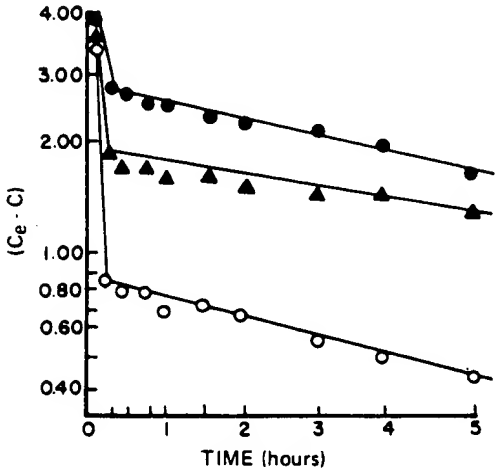
Case Study of Slowly Soluble Wax Microencapsulation [234]. *Prolonged action mechanism.* Drug is impregnated in a slowly dissolving wax.

Type and method of coating. Bleached beeswax or glycowax S-932 is mixed with drug, in a ratio of 1 part drug to 3 parts wax, and heated on a water bath to 75°C. Typical amounts were 24 gm beeswax and 8 gm sulfaethylthiadiazole (SETD). In a separate container heated to 80°C was 1 ml sorbitan mono-oleate and 1.15 ml polysorbate 80 in 400 ml of distilled water. The aqueous phase was slowly added to the wax mixture with continuous stirring at a predetermined speed until the mixture cooled to approximately 45°C. Stirring at around 300–400 rpm produced particles that were primarily in the size range of 30–100 mesh. The drug-wax particles were separated from the aqueous phase by filtration, washed with distilled water, and dried. Fractionation of the resulting particles into three mesh sizes 16–20, 30–40, and 50–60 was accomplished with USP sieves, and only the 50- to 60-mesh particles were retained for in vitro and in vivo testing.

In vitro test. Dissolution tests were conducted in a modified USP disintegration apparatus, and the results are shown in Figures 8(a) and 8(b). Drug release during the first 15 min was in direct relation to the specific surface, since the particles were assumed to have a uniform distribution of drug on the surface. After the first 15 min period, the rate of drug release varied as a function of mesh size and appeared to follow



(a)



(b)

Figure 8 (a) In vitro dissolution rates of SETD from various mesh sizes of SETD-glycowax particles in 0.1 N HCl. (●) 16–20 mesh, (▲) 30–40 mesh, $C_e - C = 0$. (b) In vitro dissolution rates of SETD from various mesh sizes of SETD-glycowax particles in alkaline pancreatin solution. (●) 16–20 mesh, (▲) 30–40 mesh, (○) 50–60 mesh. (From Ref. 234, used with permission.

first-order kinetics. The first-order dissolution appears to be due to the changing surface area.

In vivo release. Urinary excretion rates of SETD-glycowax, 50–60 mesh size range, were compared to rates for plain SETD in four humans. The 50–60 mesh size was selected because the in vitro release data were most similar to the in vitro release of a similar commercial prolonged-release SETD product. Figure 9 shows the comparison of the excretion rates for the plain SETD and the prolonged release form. The SETD-glycowax particles released 50% less drug during the first 3 h, and then the rates increased so that at the end of 24 h, 71% of the total SETD had been excreted as compared to 85% for plain SETD. Over 72 h, th

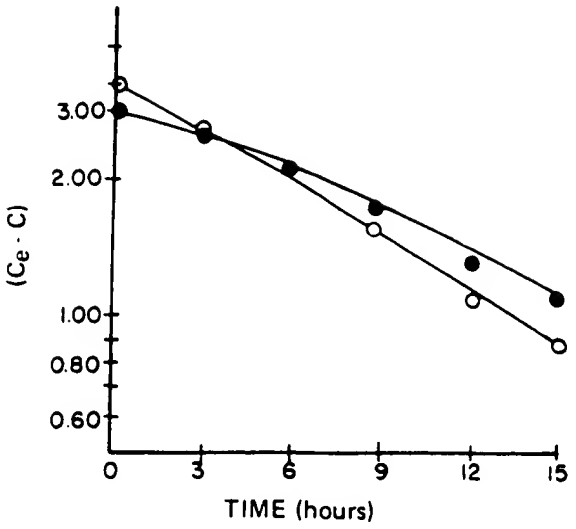


Figure 9 Average urinary excretion rates of free SETD for four humans receiving a 3.9-gm oral dose of SETD in (a) plain form and (b) SETD-glycowax combination. (•) plain SETD, (○), SETD-glycowax combination. (From Ref. 113, used with permission.)

in vivo SETD-glycowax release gave 85% excreted versus 81% in the in vitro experiment.

B. Sustained-Release Utilizing Diffusion

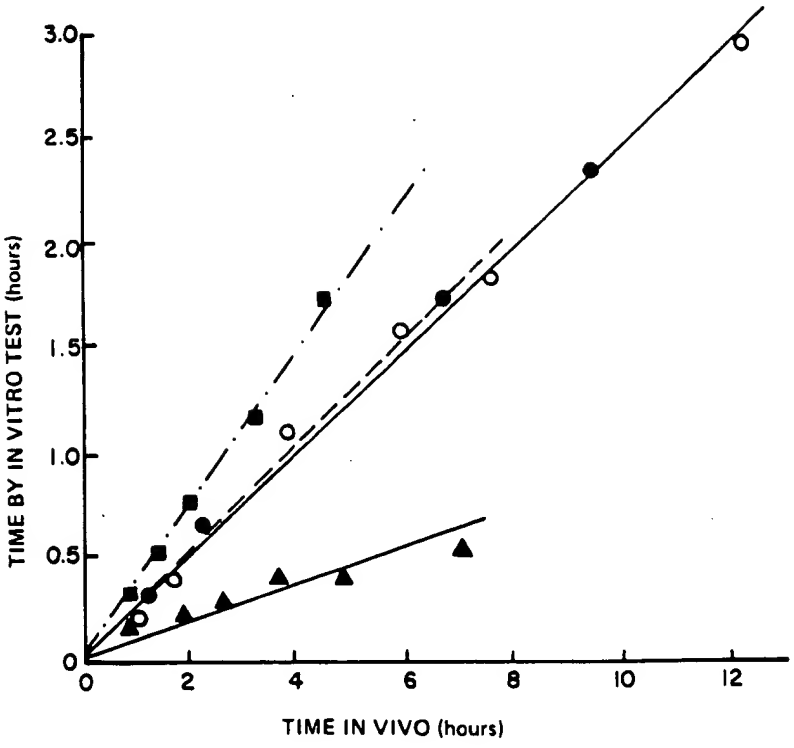
This section describes coated sustained-release systems that are distinguished from those in the previous section primarily by their mechanism of action (i.e., diffusion), as well as by their means of application and by the appearance of the final dosage form. Some of the microencapsulated materials discussed earlier released drug via a diffusion process, but the bulk of the diffusion systems will be discussed here. In the case of slowly soluble films and coatings, the reader will recall that these were generally applied via pan-coating techniques or by some form of polymerization with the end result being coated pellets or granules or microspherules that could then be compressed into tablets or placed in a capsule. The products in this section are, for the most part, press-coated films whereby a core is fed into the die and the coating material is then pressed onto it, resulting in a single-coated tablet, or they are whole tablets or particles that have been coated via air-suspension techniques. As in the previously described cases, the area and the thickness of the coating are important parameters, but they take on added importance here because diffusion of drug, either from the core or from the coating itself, must pass through the barrier represented by the coating or film. Insoluble films will thus present a rigid barrier that will act to keep the diffusion path length of drug from the tablet interior to the absorption site (outside of tablet) relatively constant. Some of the films described below are also slowly soluble, but their maintenance of constant path length is still the most important activity.

As might b expected, a lot of the research in this area has to do with the mechanics of th coating process itself, in addition to the research on developing new coatings and measuring the efficacy of administering drugs in this manner. Of course, the patent literature is filled with polymeric systems that can be used via press-coating or air-suspension techniques [154,165,240,241], and the research literature likewise [242–250]. However, since the press-coating and air-suspension processes are utilized in the pharmaceutical industry, a body of research has been developed to overcome some of the manufacturing difficulties presented by these techniques [251–254].

The original work that developed the air-suspension technique has been reported by Wurster [255,256]. This patented process is now widely used in the industry, since it is a fast, efficient way of making uniform coatings on granules and core tablets. The use of the technique for coating aspirin granules has been described by Coletta and Rubin [257]. Wood and Syarto [258] continued the same line of work involving coating aspirin with various ratios of ethylcellulose to methylcellulose. As the methylcellulose dissolved, whereas the ethylcellulose did not, the shell left behind presumably provided a restraining barrier for keeping the ASA diffusion path length constant. These authors attempted to correlate the in vitro dissolution pattern with that obtained in vivo, as shown in Figure 10. As can be seen from the correlation lines, with high-content ethylcellulose the in vitro/in vivo correlations are good. As the percent of methylcellulose in the coating is increased, the correlation falls off, and this points out the fallacy of using in vitro data alone to predict in vivo performance of these tablet coatings.

Many researchers have, of course, looked at the polymeric materials used in the coating processes with an eye to developing better, more durable, and more easily applied coats. Polyvinylpyrrolidone-acetylated monoglyceride [244], styrenemaleic acid copolymer [245], hydroxypropylcellulose-polyvinylacetate [259,260], and many other polymers have been studied for their value as enteric coatings [243,248,250] and for use in developing sustained-release preparations [246–248]. Enteric coating is a subject dealt with elsewhere in this text, but the application of enteric coats can be accomplished via press-coating and air-suspensions techniques just as described here.

Donbrow and Friedman [259] reported the release of caffeine and salicylic acid from cast films of ethylcellulose and the release rates were found to agree with both the classic first-order equation (log drug retained in film versus time) and with the diffusion-controlled release models (drug release linearly related to square root of time) as developed by Higuchi [260]. More stringent mathematical treatment of their data resulted in the diffusion-controlled release model being most appropriate to describe their data. Borodkin and Tucker [261,262] also used cast films of drug in hydroxypropylcellulose, studying the release of salicylic acid, pentobarbital, and methapyrilene. These drugs were released according to the same diffusion-controlled model described above. Further work to modify the system resulted in zero-order drug release obtained by laminating a second film without drug to the releasing side of the film containing drug. Thus, the nondrug layer functions as a rate-controlling membrane, and the drug-containing film serves as a reservoir. In vitro zero-order drug release for the three species mentioned was demonstrated using this technique.



Composition and Characteristics of Test Delayed-Release Aspirin Products Used in This Study

	Code			
	134B	134C	152	138
Ratio ethyl to methylcellulose	75/25	25/75	82.5/17.5	100/0
Aspirin mesh size	−20	−40	−20+40	−20+40
Amount of coating (wt %)	2.7%	4.8%	6%	6%
Tablet disintegration time (sec)	40−60	25−35	3	3
Aspirin content	5 gr	5 gr	5 gr	5 gr
Cornstarch	0.87 gr	0.90 gr	0.96 gr	0.96 gr
Talc	−	−	0.13 gr	0.13 gr

Figure 10 Correlation between in vivo absorption and in vitro release rates for corresponding fractions of total salicylate considered. (■) 152, (●) 138, (▲) 134C, (○) 134B. (From Ref. 258, used with permission.)

Since the technique described in this section can be used to coat core tablets or granules, it is conceivable that many of the clinical studies described earlier could be applicable in this case. However, a very good clinical study of the Sinusule sustained-release dosage form has been described [263]. This product is somewhat different from the others examined thus far in that the film applied to the granules actually functions as a microdialysis membrane. Thus, one need not worry about the acidity of the gut, the digestive process, nor the contents of the gut. The only requirement is that there be fluid in the gut. The fluid, primarily water, passes through the dialysis membrane into the sphere and dissolves the granule of drug. This drug then diffuses through the intact membrane at a rate proportional to the permeability of the membrane, the mobility of the drug molecule, and the concentration of the drug within the hydrated microdialysis cell. When this product was tested in patients having hay fever, upper respiratory infection, and miscellaneous respiratory allergies, good to excellent results with a minimum of side effects were reported for a large majority of the test population. This novel sustained-release dosage form is not marketed anymore.

Case Study of Duffusion-Controlled Coating [261]

PROLONGED ACTION MECHANISM. Drugs are dispersed in a water-soluble polymeric coating which, when subjected to an aqueous environment, allows slow diffusion of drug into the leaching fluid.

TYPE AND METHOD OF FILM FORMATION. Hydroxypropylcellulose, average molecular weight of 100,000, having viscosity 75–150 cps as a 5% water solution, and polyvinylacetate, average molecular weight 500,000, having viscosity 90–110 cps as an 8.6% benzene solution, were used. Drugs were pentobarbital, salicylic acid, and methapyrilene. The films were cast from a solution containing 10% solids (drug plus polymer), using methylene chloride/methanol mixture (9:1) as the solvent. The polymers were added as dry powders, as was salicylic acid, while the pentobarbital and methapyrilene were added from stock methylene chloride solutions. Films were cast from the solutions at various wet thicknesses (0.64–2.54 mm) using a knife on Teflon-coated plate glass. The films were allowed to air dry at least 48 h before evaluation. The percent drug in the dry film was calculated from the ratio of drug and polymer weights used.

MECHANISM OF DRUG RELEASE. Release of drug from a matrix can be either via a first-order process or via a diffusion-controlled process. Which release is operative can be ascertained by appropriate data treatment. First-order release would be a linear plot following the normal first-order equations, whereas a diffusion-controlled process should result in an S-shaped curve following the equation

$$Q = \sqrt{\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t} \qquad (13)$$

where Q = amount of drug released per unit area of tablet exposed to solvent

D = diffusion coefficient of drug in the permeating fluid

ε = porosity of the matrix

τ = tortuosity of the matrix

A = concentration of solid drug in the matrix

C_S = solubility of drug in the dissolution medium

t = time

The above equation is more commonly expressed as

$$Q = k_H t^{1/2} \tag{14}$$

where $k_H = \Sigma D[(2A - C_S)C_S]^{1/2}$ for plotting purposes.

IN VITRO TEST. Rectangular films measuring 2.2 × 4.0 cm (8.8 cm^2) were cut using a razor blade with a microscope cover glass as a template. The film was weighed and its thickness was measured at all four corners and the center with a micrometer. A thin coating of high-vacuum silicone lubricant was applied to a 2.54 × 7.62 cm microscope slide and the film was pressed into the slide, making sure that all edges adhered and no lubricant touched the exposed surface. The slide was placed at an angle into a 250-ml beaker in a 37°C-water bath containing 200 ml of pH 7 buffer preheated to 37°C. A nonagitated system was used to eliminate turbulence effect on release rate and to maintain film integrity. Periodic assay samples ($\sim$10 min^{-1}) were obtained by removing the slide, stirring the solution, and pipetting a 5-ml sample, and then reimmersing the slide with film into the buffer solution. Beakers were covered throughout the length of the runs (7 h at least and 31 h in the extreme for slow-releasing films) to prevent evaporation. The samples were assayed by ultraviolet (UV) spectrophotometry at 240 nm for pentobarbital in 0.1 N NH_4OH, at 312 nm for methapyrilene in 0.1 N HCl, and at 297 nm for salicylic acid in 0.1 N NaOH.

Table 13 shows the results of comparing the drug release to first-order and square root of time equations. When these data were evaluated to determine which equation gave best fit, the correlation coefficients for the best statistical lines and the lag times (time intercept extrapolated to Q = 0) were used as the principal criteria. Although the correlation coefficients looked good for either mechanism, when these types of data are plotted out, as is shown in Figure 11, the curvature in the first-order mechanism was evident. This indicated that the Q versus $t^{1/2}$ relation more readily described the mechanism. Correlation coefficients were generally greater than 0.995 for this type of plotting and deviations, when they occurred, were random rather than the result of curvature. Linearity in release held through 75–80% of drug release when a constant concentration gradient was operative.

The effect of film thickness on the rate of drug release for pentobarbital is shown in Table 14. These results indicate that the release rate constant, k_H, is independent of film thickness. However, film thickness will affect the duration of drug release, as is shown in th last column where $t_{1/2}$ represents the time, in minutes, for 50% of the drug in each particular film to be released.

Tables 15–17 show the effects of varying polymer ratio on the release rate, k_H, for the drugs methapyrilene, salicylic acid, and pentobarbital, respectively. In general, an acceleration of release rate can be obtained

Table 13 Comparison between First-Order and Q versus $t^{1/2}$ Treatments of Pentobarbital Release Rate Data

Drug concentration (%)[a]	Hydroxypropylcellulose/ polyvinylacetate ratio	Number of runs	First-order		Q versus $t^{1/2}$	
			t_{lag} (min)[b]	Correlation coefficient	t_{lag} (min)[b]	Correlation coefficient
36.4	10:0	4	−3.2	0.996	3.1	0.997
18.2	10:0	4	−14.0	0.957	2.6	0.993
18.2	9:1	2	−9.8	0.986	2.8	0.996
18.2	8:2	2	−6.5	0.986	2.3	0.993
18.2	6:4	2	−84.0	0.982	1.4	0.996
18.2	4:6	4	−142.0	0.983	0.3	0.998
18.2	2:8	4	−176.0	0.981	0.6	0.998
18.2	1:9	4	−176.0	0.982	0.7	0.998
18.2	0:10	3	−214.0	0.979	1.0	0.997
9.1	0:10	4	−199.0	0.981	1.3	0.990

[a]Weight of drug per weight of dry film.

[b]All t_{lag} and correlation coefficient values expressed are mean values.

Source: From Ref. 259, used with permission.

Table 14 Effect of Film Thickness on Pentobarbital Release Rate Constant and Half-Life

Drug concentration (%)[a]	Hydroxypropylcellulose/ polyvinylacetate ratio	Wet film thickness setting (mm)	Dry film thickness (μm)[b]	k_H (mg cm^{-2} $min^{-1/2}$)	Correlation coefficient	$t_{1/2}$ (min)
36.4	10:0	0.64	44.0 ± 1.1	0.33	0.996	14.8
		1.27	56.2 ± 2.1	0.29	0.996	25.2
		1.91	100.2 ± 4.6	0.33	0.998	49.8
		2.54	109.3 ± 3.3	0.32	0.998	60.2
18.2	4:6	0.64	61.4 ± 4.9	0.032	0.999	360
		1.27	113.2 ± 9.9	0.034	0.999	1,280
		1.91	145.0 ± 8.0	0.034	0.999	2,850
		2.54	204.2 ± 3.1	0.037	0.997	3,850
18.2	1:9	0.64	76.8 ± 1.2	0.0101	0.996	8,520
		1.27	118.4 ± 2.6	0.0102	0.999	19,200
		1.91	202.8 ± 2.2	0.0101	0.998	50,900
		2.54	268.0 ± 2.4	0.0102	0.998	83,600

[a]Weight of drug per weight of dry film.

[b]Thickness = mean ± standard deviation of five measurements.

Source: From Ref. 259, used with permission.

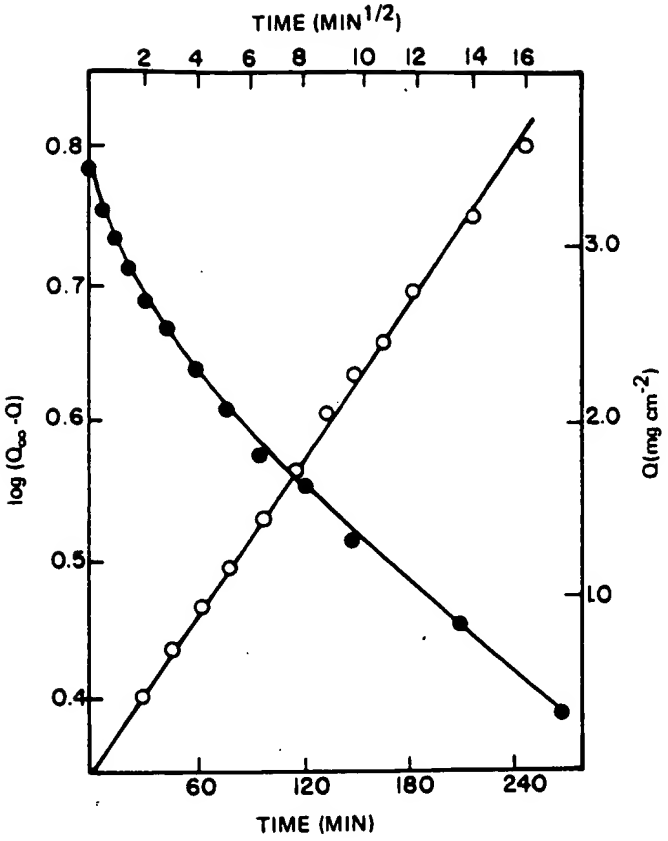


Figure 11 Comparison between first-order release treatment and Q versus $t^{1/2}$ treatment of data from a film containing 26.3% methapyrilene at a 5:5 ratio of hydroxypropylcellulose/polyvinylacetate. (•) log (Q_∞ − Q) versus t, and (○) Q versus $t^{1/2}$. (From Ref. 259, used with permission.)

by increasing the proportion of hydroxypropylcellulose to polyvinylacetate. The large variations in the $t_{1/2}$ values reflect the changes in the polymer ratio and, in addition, the changes in film thickness.

C. Sustained-Release Utilizing a Combination of Dissolution and Diffusion

The products to be discussed in this section are those that provide the sustaining portion of the dose in some sort of relatively insoluble core that has been impregnated with the drug. This core is almost always coated and the coat contains that portion of the dose meant for immediate release upon dissolution of the coat in the stomach. Once this occurs, the gastrointestinal fluids are free to permeate the core and thus slowly leach out the drug. Of course, the possibility exists that the core material can sometimes be dissolved slowly to provide drug, but this is usually not the the case. The diffusion of drug out of the core is the major mechanism for providing drug in sustained release form. In these preparations the area over which diffusion cocurs remains relatively constant (especially if no core dissolution occurs) and the amount of drug is in excess. The

Table 15 Effect of Hydroxypropylcellulose/Polyvinylacetate Ratio on the Release Rate from Films Containing 26.3% Methapyrilene

Hydroxypropyl-cellulose/ polyvinylacetate ratio	Dry film thickness (μm)[a,b]	k_H (mg cm^{-2} $min^{-1/2}$)	Correlation coefficient	$t_{1/2}$ (min)
10:1	210 ± 7.4	0.549	0.999	33
9:1	210 ± 6.5	0.593	0.997	28
8:2	216 ± 9.1	0.497	1.000	42
7:3	181 ± 7.8	0.272	0.995	99
6:4	218 ± 4.4	0.217	0.998	226
5:5	208 ± 4.6	0.225	0.999	190
4:6	142 ± 4.5	0.191	0.997	124
3:7	157 ± 3.3	0.094	0.998	630
2:8	136 ± 3.3	0.089	0.999	523
1:9	131 ± 6.0	0.075	0.998	681
0:10	185 ± 0.9	0.074	0.996	1404

[a]Thickness = mean ± standard deviation of five measurements.

[b]All films cast using a wet thickness setting of 2.54 mm.

Source: From Ref. 259, used with permission.

factor that changes, in this case, is the path length term in Fick's first law. As more drug diffuses out of the core, the permeating gastrointestinal fluid must travel an increasingly longer and more tortuous path to get to the remaining drug. The dissolved drug, in turn, has to diffuse out via the same altered pathways. Thus, a tortuosity factor must be included in the equation to describe release.

One of the earliest of these core-type products to be described was Duretter, developed by Sjogren and Fryklof [264] in Sweden. It differs from other core-type tablets, such as Ciba's Lontab, in that the core is produced by directly compressing a granulate of the drug and an insoluble plastic material so that a coherent, porous skeleton of the matrix material forms around the drug. In core tablets such as Lontab, on the other hand, the drug is incorporated into the melted matrix material and this is then spread out to dry. After drying it is granulated, and this granulation is then compressed into the core tablet [265]. In the final result the differences in manufacturing are not evident, and the release patterns of drug from these species are similar in many respects.

The release rate and absorption characteristics of various drug incorporated into a plastic matrix type of tablet have been extensively studied. Sjogren and Ostholm [266] studied the release of nitroglycerin, lobeline hydrochloride, ^{82}Br-labeled ammonium bromide, creatinine, potassium

Table 16 Effect of Hydroxypropylcellulose/Polyvinylacetat Ratio on th Releas Rate from Films Containing 20.0% Salicylic Acid

Hydroxypropyl-cellulose/ polyvinylacetate ratio	Dry film thickness (μm)[a,b]	k_H (mg cm^{-2} min$^{-1/2}$)	Correlation coefficient	$t_{1/2}$ (min)
10:0	189 ± 2.8	0.403	0.997	28
9:1	223 ± 5.6	0.336	0.997	57
8:2	210 ± 0.9	0.328	0.993	53
7:3	229 ± 2.5	0.241	0.998	116
6:4	209 ± 6.6	0.216	0.984	120
5:5	204 ± 7.9	0.175	0.997	175
4:6	145 ± 0.5	0.115	0.997	206
3:7	156 ± 3.4	0.122	0.997	210
2:8	181 ± 7.9	0.112	0.998	338
1:9	222 ± 4.3	0.073	0.998	1190
0:10	172 ± 1.8	0.057	0.996	1040

[a]Thickness = mean ± standard deviation of five measurements.

[b]All films cast using a wet thickness setting of 2.54 mm.

Source: From Ref. 259, used with permission.

penicillin V, and dihydromorphinone hydrochloride both in vitro and in vivo, in cats and humans. They noted good correlations between in vitro and in vivo results, both in blood levels of active drug, and also when monitoring a particular pharmacological effect produced by the drug, although of course in vivo determination of release rate was much more difficult to estimate. In a continuation of this type of study, Sjogren and Ervik [267] developed an automatic spectrophotometric method for studying continuous release rates of quinidine bisulfate and ephedrine hydrochloride from Duretter plastic matrix tablets and obtained highly reproducible results.

The complex interplay between the processes of release and degradations of substances dispersed in polymeric matrixes has been described in great detail by Collins and Doglia [268]. Although their discussion is of general nature, the analogy to drugs and pharmaceutical systems is apparent. El-Egakey et al. [269] and Asker et al. [270–272] have delv d into the in vitro release of drugs from polymeric matrixes and granulations. In the case of water-soluble drugs, merely granulating the drug with th melted matrix material will provide suitable sustained release of drug, whereas with more water-insoluble drugs, a coating providing drug for immediate releas and absorption takes on increasing importance as the degree of water solubility decreases. Obviously, the limiting cas her is a drug with virtually no water solubility. This drug w uld not need t

Table 17 Effect of Hydroxypropylcellulose/Polyvinylacetate Ratio on the Release Rate from Films Containing 18.2% Pentobarbital

Hydroxypropylcellulose/ polyvinylacetate ratio	Wet thickness setting (mm)	Dry film thickness (μm)[a]	k_H (mg cm^{-2} $min^{-1/2}$)	Correlation coefficient	$t_{1/2}$ (min)
10:1	1.27	98 ± 5.4	0.225	0.995	20
9:1	2.54	163 ± 3.4	0.224	0.995	57
8:2	1.27	87 ± 6.4	0.178	0.987	25
6:4	2.54	236 ± 7.1	0.0767	0.997	1.010
4:6	1.91	145 ± 8.0	0.0342	0.999	2.280
2:8	1.27	94 ± 1.9	0.0161	0.999	3.630
1:9	1.27	118 ± 2.6	0.0102	0.999	19.200
0:10	1.91	210 ± 15.5	0.0260	0.998	6.960

[a]Thickness = mean + standard deviation of five measurements.
Source: From Ref. 259, used with permission.

be placed in a special sustained-release dosage form, since it is inherently long acting by nature of its poor aqueous solubility. Of course, the method of preparation of the granulating materials, the choice of in vitro dissolution media, and the plastic matrix material chosen will all have an influence on release of the drug from the sustained-release dosage form.

Water-soluble drugs dispersed in hydrophilic matrixes were studied by Lapidus and Lordi [273]. Their results indicate that chlorpheniramine maleate dispersed in methylcellulose is release-rate controlled mostly by drug diffusivity rather than by polymer dissolution and water permeability. Thus, even for drugs formulated in a water-soluble matrix, one which would itself be subject to erosion and absorption in the body, the determining factor in providing sustained release is still diffusion of the drug out of the matrix. This important fact was further elaborated on by Huber et al. [274] for hydrophilic gums versus the matrix material. In this case, the mechanism of prolonged release was determined to be drug diffusion from, and eventual attrition of, a gel barrier at the periphery of the tablet core.

A modification of this type of matrix tablet was described by Javaid et al. [275]. They used a lipase-lipid-drug system to provide sustained release whereby the erosion of the matrix due to the hydrolytic action of lipase on the substrate was the desirable first step in obtaining release of the drug for absorption. Accelerators of lipase activity, such as calcium carbonate or glyceryl monostearate, could be used to tailor make a sustained-release tablet to provide a desired release profile. Javaid and Hartman [276] then tested these enzyme-substrate-drug tablets in dogs, and the action of lipase to control drug release was confirmed. Tablets containing lipase consistently gave higher and more uniform blood levels of drug than those without, as is evident in Figure 12. It is apparent that the enzyme-substrate type of matrix tablet has potential for commercial use in providing sustained release.

The type of plastic matrix sustained-release dosage form that has been investigated the most extensively is undoubtedly that of a drug dispersed in an insoluble, inert matrix [3–5,10,15,18,278–285]. The kinetics of release and the methods of treating the matrix tablets have been reported

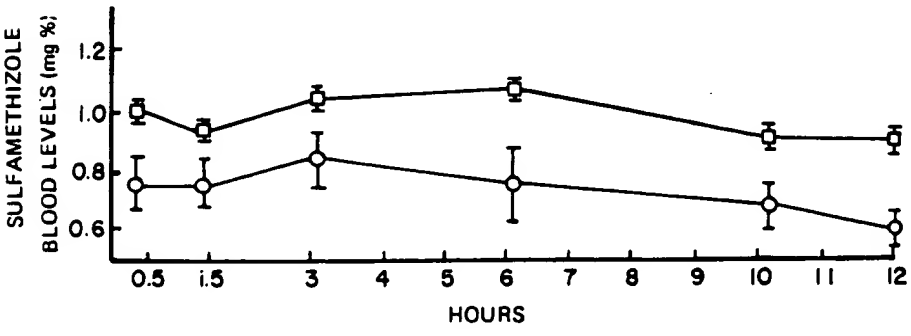


Figure 12 Average sulfamethizole blood levels (mg%) in dogs after receiving tablets containing 100% drug in drug-lipid granules with 5% glyceryl monostearate. (□) tablets with lipase and (○) tablets without lipase. Standard errors are plotted around the averages. (From Ref. 276, used with permission.)

by Farhadieh and coworkers [277,279] for drugs dispersed in a methyl acrylate-methyl methacrylate matrix. As seen in Table 18, treatment of the tablets by exposure to acetone vapor results in a significant decrease in the release rate of drug from the matrix. This, coupled with control of the treatment temperature, allowed production of sustained release tablets with highly reproducible release rates. An investigation of the problems that could result from chewing an insoluble matrix was the subject of a paper by Ritschel [280]. If the drug is incorporated in the pores and channels of a matrix tablet, potential toxicity could occur if the tablet was inadvertently chewed by the patient, since this would result in the release of large quantities of the drug. For drugs with a narrow therapeutic range, such as nitroglycerin, this could be a problem. When the drug was dissolved directly into the plastic matrix material, the problem is alleviated since even with mastication the drug is not free to be absorbed.

Sjuib et al. [281,282] continued the work of Higuchi on the study of drug release from inert matrixes. The original physical model described by Higuchi and coworkers [286–294] was tested for binary mixtures of acidic drugs and also for binary mixtures of amphoteric drugs. Analysis showed that the physical model could describe the experimental data quite well and also pointed out that the precipitation of the drug in the matrix during release into alkaline media, such as might be encountered in the intestinal fluids, has to be considered more important than theories involving supersaturation of the drug in the matrix. The mathematics of both matrix-controlled and partition-controlled drug release mechanisms were elucidated by Chien et al. [285]. They pointed out that the transition that occurs between the two processes is dependent on the magnitude of the solution solubility of the drug and, via a series of equations, indicated that this term dictates the mechanism and rate of drug release from the polymer matrix.

Other research in the area of drug release from insoluble matrix tablets has found that the square root of time relation originally proposed by Higuchi [260] described the advance of the solvent front into the tablet [283]. Compression force was not a major factor and drug release was, of course, proportional to the total surface area.

As can be seen from the above cited work, a tremendous amount of time and effort has been expended to elucidate and quantify the factors that are important in obtaining controlled-release from plastic matrix-type tablets. The perturbations introduced by varying diluents, matrix material, and so on are all important in describing the in vitro release of drug from these tablets, and presumably are equally important in describing the in vivo release rates. However, we would be remiss if the clinical evaluation of these types of dosage forms are not included here, since the literature is full of examples in which systems showing good in vitro possibilities were unsuccessful in an actual clinical trial.

The effects of gastric emptying time and intestinal peristaltic activity on the absorption of aspirin from a sustained-release tablet containing coated particles in a hydrophilic gel type matrix and conventional aspirin tablets were described by Levy and Hollister [295]. The lag times in the absorption profiles reported were undoubtedly due to the time required for transfer of the dosage form from the stomach to the intestine. The authors point out the pitfalls of plotting averaged individual absorption data versus time and how this could lead to erroneous assumptions about whether a dosage form is a good candidate for sustained release or not.

Table 18 Effect of Acetone Vapor Pressure on the Release Rate of Drug from 100-mg Sodium Pentobarbital Tablets at Three Different Temperatures

Temperature	Acetone vapor pressure (mmHg)	Acetone absorbed (mg/tablet)	ϵ	τ	$k \times 10^1$ (g cm^2 sec$^{-1/2}$)	$t_{1/2}$ (hr)
Untreated tablets		0	0.575	9.24	5.38	3.38
37°	217	16.2	0.567	11.5	4.93	4.03
	244	19.0	0.559	13.3	4.64	4.54
	267	25.3	0.559	19.7	3.87	6.52
	307	30.7	0.535	52.2	2.44	16.4
	347	44.9	0.530	154.9	1.43	47.8
34°	217	18.4	0.560	12.2	4.79	4.26
	244	22.5	0.51	16.6	4.19	5.57
	267	27.9	0.539	43.2	2.67	13.7
	307	39.7	0.534	198.2	1.26	61.5
31°	217	26.1	0.551	18.6	4.01	6.08
	244	29.3	0.540	36.4	2.91	11.5
	267	32.8	0.528	86.2	1.93	26.2

Source: From Ref. 277, used with permission.

Individual absorption data that results in a first-order plot can often appear to be zero-order, indicating good sustained release, when such data are averaged. Thus, it is necessary to look at the data for each individual in the test population when assessing sustained-release characteristics.

Nicholson et al. [296] described the blood and urine levels obtained in humans following ingestion of sustained-release tablets. It was noted that the sustained-release tablets gave less variation between maximum and minimum blood level concentrations and more uniform urinary excretion rates than conventional release tablets. Theophylline aminoisobutanol, administered in a tablet containing a sustained-release core having a matrix of hydrophilic gums, a delayed barrier coat on the core, and an outer coat containing the drug for immediate release was investigated by Kaplan [297]. Both in vitro and in vivo results were obtained and the blood level data correlated well. Although differences were noted in the urinary data, no explanation was tendered other than noting that these differences have been reported previously. The in vivo absorption and excretion of radioactively tagged [10-^{14}C]pentylenetetrazol was studied by Ebert et al. [278]. Human volunteers were given either a single dose of sustained-release insoluble matrix tablets or three divided doses of conventional tablets. It was shown that the sustained-release form gave absorption and excretion patterns similar to those obtained in the divided dose case.

As noted earlier in the section on coated granules, the earliest commercially available sustained-release preparations available for clinical trials seem to be those providing antihistamines [166,167,298,299]. Such research has led to clinical trials of sustained-release triethanolamine trinitrate [300] for use in angina pectoris. The drug was provided in a plastic matrix that leached out drug over a 7- to 8-h span. Patients reported no undesirable side effects and the frequency and severity of attacks were diminished in 80% of those tested.

De Ritter [301] used urinary excretion rates to evaluate nicotinic alcohol tartrate administered to humans via Roche's Roniacol Timespan matrix tablets. This dosage form uses a coating containing drug to provide the immediate release portion of the dose and the sustaining portion is provided by erosion and/or leaching of the insoluble matrix in the gastrointestinal tract. The results indicate good correlation of in vitro and in vivo release rates, and the drug is as completely available in this form as in conventional tablets. In addition, the intense flushing caused by non-sustained-release tablets is absent with the sustained release form.

The tension-relieving and sedative properties of pentobarbital sodium, administered via conventional capsules and Abbott's Gradumet plastic matrix sustained-release form, were clinically evaluated by Cass and Frederik [302]. Although the grading system employed was qualitative in nature, the results indicated that the Gradumet form was useful in providing daytime tranquilization and it was virtually free of untoward side effects.

The Gradumet matrix dosage form has also been evaluated for treatment of iron deficiency an mia via the sustained release of ferrous sulfate [303,304]. In all cases, the hematocrit and hemoglobin responses were virtually identical whether the non-sustained-release form or the matrix tablet was administered. However, the incidence of reported gastrointestinal upset due to ferrous sulfate, an important problem because more iron is absorbed by fasting patients while at the same time causing more gastrointestinal distress, was greatly diminished when the dose was given

as a sustained-release tablet. Crosland-Taylor and Keeling [305] formulated their own sustained-release ferrous sulfate tablets in an inert polymer matrix and they added $[^{59}Fe]SO_4$ as a marker to aid in evaluation. They point out that the previously mentioned hematocrit and hemoglobin responses are relatively insensitive means for comparing conventional and sustained-release tablets, and their results indicate variable absorption from sustained-release forms. They found no real advantage, even in the area of management of side effects, to the use of sustained-release forms of ferrous sulfate. It is not clear, then, whether there is any significant advantage to providing oral hematinics in sustained-release form.

Owing to the many unpleasant side effects of oral potassium supplementation, such as extremely salty taste and severe gastrointestinal upset, the past few years have seen a need for a slow-release potassium-providing product. Slow-K, marketed by Ciba, is the best example of this type of product. The sugar-coated wax matrix contains 600 mg of potassium chloride that leaches out gradually over a 4- to 6-h period. Tarpley [306] studied the patient acceptability of this product as well as its ability to maintain normal serum potassium levels in clinical trials comparing it to oral potassium liquid preparations. His findings indicate that both types of products maintain serum K^+ levels, but the sustained-release tablet gives much less incidence of nausea, abdominal pain, cramps, diarrhea, etc., and, of course, since it has little or no taste before being swallowed, it was much more palatable and acceptable to all the patients involved.

As was noted earlier, aspirin has been tested for delivery via every new dosage form developed for the past 20–25 years. Here, as in the case of oral antihistaminics, the simple arithmetic of profit and loss statements has compelled pharmaceutical firms to develop sustained-release aspirin preparations [307]. The market is largely due to the vast numbers of arthritics who need a preparation that will provide aspirin throughout the night and eliminate morning stiffness, the most common plight of arthritis sufferers. Many products have been extensively tested in clinical trials as well.

Wiseman and Federici [308] have developed a sustained-release aspirin tablet utilizing the matrix principle. By carefully monitoring both in vitro and in vivo data, the authors were able to fashion a product that gave constant plasma salicylate concentrations on chronic administration. Wiseman [309] then extended the tests to the clinic where highly reproducible, stable plasma salicylate concentrations were attained that overcame the fluctuations due to multiple dosing of conventional tablets. The stable levels do not exhibit the peaks in serum salicylate levels shown by conventional tablets; therefore the incidence of gastrointestinal upset was reduced and the valleys, or low points, were eliminated, thus providing therapeutic levels of salicylate throughout the night. Harris and Regalado [310], however, compared conventional and sustained-release aspirin for their ability to provide relief to patients in order that the latter might perform simple tasks requiring phalangeal dexterity. They reported no difference between the two types of tablets, but a majority of the patients preferred the sustained-release form. The inference here is that the sustained-release product gave relief throughout the night and did not cause the unpleasant gastrointestinal side effects, thus contributing to the patient's preference. Also, the convenience of eliminating frequent daytime doses was significant in the preference for sustained-release aspirin.

These are just a few examples of the benefits obtained from providing aspirin in a sustained-release matrix tablet and of sustained-release dosage forms for administering aspirin, in general. The recent flourish of timed release and double- or triple-strength aspirin tablets to the market attests to the desirability and, consequently, the profitability of long-acting aspirin preparations.

Case Study of Combination Dissolution–Diffusion Coating [280]

PROLONGED ACTION MECHANISM. Coated or uncoated plastic matrix tablets. Solvent dissolves the coat containing the initial dose and drug is leached out of the plastic core to maintain therapeutic levels. A diagrammatic structure of the tablet is shown in Figure 13 for the drug combination nitroglycerin and proxyphylline.

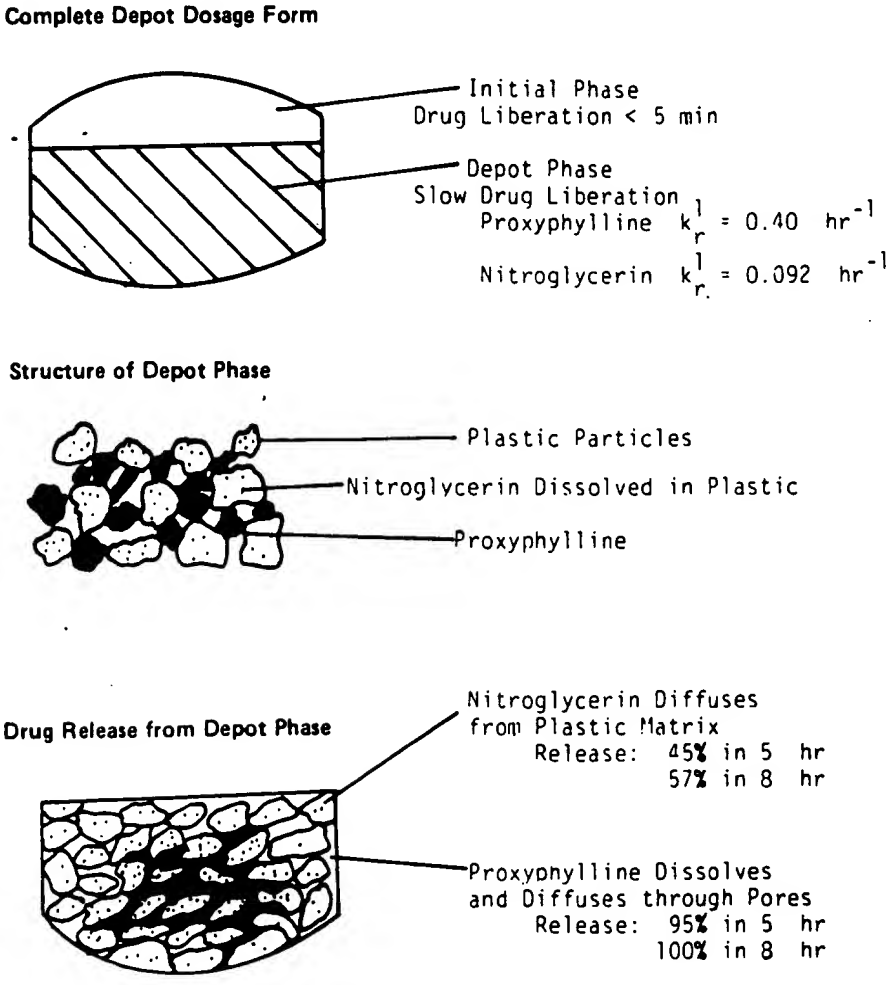


Figure 13 Diagrammatic structure of the peroral sandwich tablet with timed release and its release characteristics. (From Ref. 280, used with permission.)

Table 19 Pharmacokinetics of Proxyphylline in a Timed-Release Tablet into Which Nitroglycerin Was to Be Incorporated

Biological half-life	$t_{1/2} = 4.3$ (h)
Absorption rate constant	$K_a = 1.3$ (h^{-1})
Elimination rate constant	$K_{el} = 0.163$ (h^{-1})
Time to reach peak	$T_p = 2.5$ (h)
Therapeutic concentration to maintain for 12 h	$B_D = 0.8$ (mg/100 L)
Single dose producing desired blood level	$D_B = 0.48$ (g)
Liberation constant from depot phase	$k_r^1 = 0.4$ (h^{-1})
Equation for plasma concentration	$C = 11.5 \cdot e^{-0.153t} - 12.5 \cdot e^{-1.3t}$
Percent absorbed relative to the amount ultimately absorbed	$\frac{AT}{A}, 100 = CT + K_{el}TC_{DT}$
	Percent after 0.25 h = 35.6
	0.5 h = 45.5
	1.0 h = 74.4
	1.5 h = 100.0

Maintenance dose

$$D_M = \frac{K_{el}B_D}{k_r^1} = 0.312 \text{ (g)}$$

Initial dose

$$D_i = D_B - D_M \cdot (k_r^1 T_p) = 0.177 \text{ (g)}$$

Total dose per tablet

$$W = D_B - D_M \cdot (k_r^1 T_p) + \frac{K_{el}B_D}{k_r^1} = 0.489 \text{ (g)}$$

Source: From Ref. 280, used with permission.

EXPERIMENTAL DESIGN. The pertinent design variables for this dosage form are shown in Table 19. Nitroglycerin was dissolved in 1:1 alcohol/acetone solvent and was then impregnated in plastic granules of either polyvinylchloride, ethylcellulose, polyamide, polyvinylacetate, or polyacrylate. The plastic granules must be partly soluble in the alcohol/acetone solvent. The solvent was evaporated and the plastic mass containing nitroglycerin with screened to particle sizes of 0.5–1.0 mm. These particles were then mixed with proxyphylline and compressed into tablets. The final two-layered tablet contained 0.2 mg nitroglycerin and 180 mg proxyphylline in the immediate-release coat and 5 mg of nitroglycerin, in a solid–solid solution matrix with the plastic material, and 310 mg of proxyphylline in the matrix pores, constituted the sustaining section.

IN VITRO TEST. The results of in vitro testing of the tablet are shown in Figure 14. The solid and open circles indicate that good sustainment is achieved with this tablet and that if accidental mastication occurs, as illustrated by the other lines in the figure, some of the sustaining effect is lost. Proxyphylline was released with an apparent first-order rate of $k_r^1 = 0.40\ h^{-1}$ and nitroglycerin had $k_r^1 = 0.092\ h^{-1}$. The data indicate that the proxyphylline, incorporated into the pores of the matrix, dissolves as soon as the artificial gastrointestinal fluid enters the pores resulting 95% release within 5 h. Nitroglycerin, because it is dissolved into the plastic matrix as a solid–solid solution, must diffuse through the plastic material into the artificial gastrointestinal fluid. Consequently, its release is much slower, resulting in only about 45% being released within 5 h.

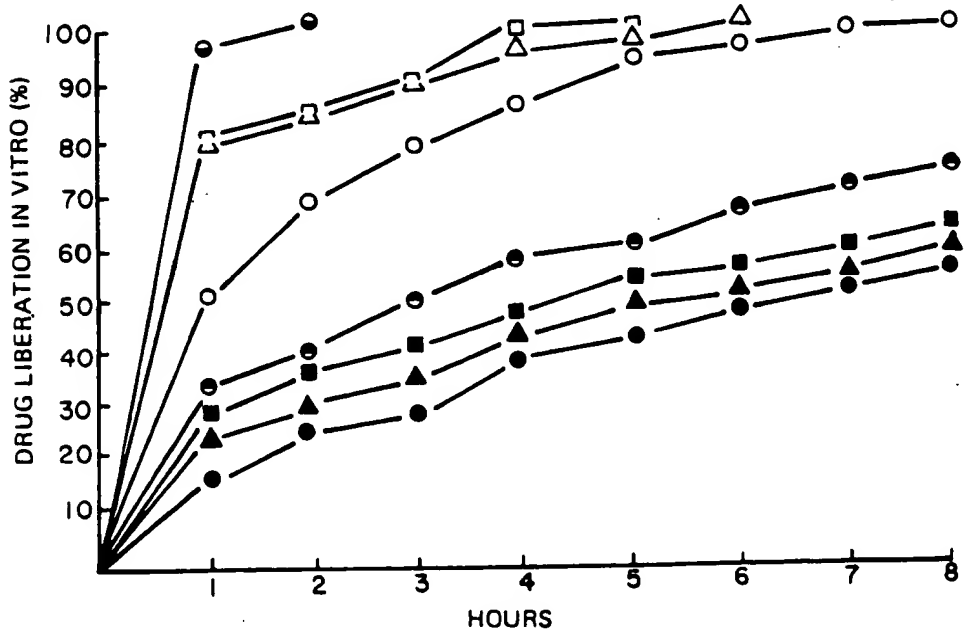


Figure 14 In vitro drug liberation. Proxyphylline: (○) intact tablet, (△) cut into two parts, (□) cut into four parts, (●) powdered. Nitroglycerin: (●) intact tablets, (▲) cut into two parts, (■) cut into four parts, (●) powdered. (From Ref. 280, used with permission.)

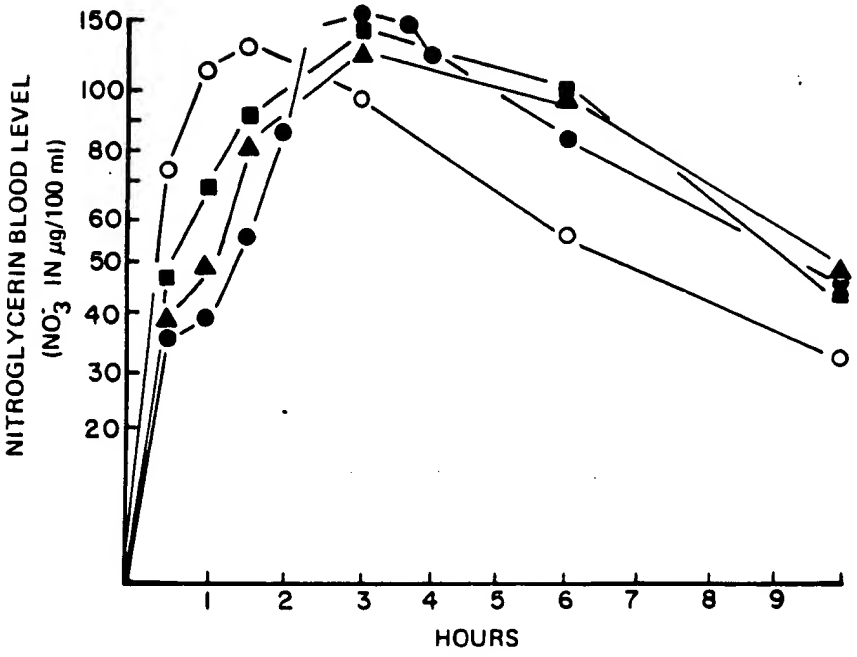


Figure 15 Nitroglycerin blood level after peroral administration. (●) intact tablet, (▲) cut into two parts, (■) cut into four parts, and (○) powdered and masticated. (From Ref. 280, used with permission.)

Although the in vitro release study showed that in divided tablets the prolonged activity was essentially lost for proxyphylline, the nitroglycerin still maintained its sustaining activity.

IN VIVO TEST. Figure 15 shows the results of the in vivo testing for sustained release of nitroglycerin in these products. These are the mean curves from three human subjects. As stated by the author, three subjects is too small a population to generate definitive statistics, so that this study should be repeated with more subjects. The results did indicate good sustained release of nitroglycerin and served as a useful experimental guide.

D. Sustained Release Utilizing Osmosis

An example of sustained release through osmosis is the so-called osmotic tablet [11,12,311]. The coating in this case is just a semipermeable membrane that allows penetration of water, but not drug, to dissolve its contents. The dissolved drug plus diluents establishes an osmotic pressure and forces drug solution to be pumped out of a small hole in the tablet coating. The rate of this drug pumping can be controlled through core composition, coating material, and delivery orifice. A pictorial representation of the osmotic tablet is shown in Figure 16.

The tablet imbibes fluid through its semipermeable membrane at a constant rate determined by membrane permeability and by osmotic pressure of the core formulation. With the system at a constant internal volume, the

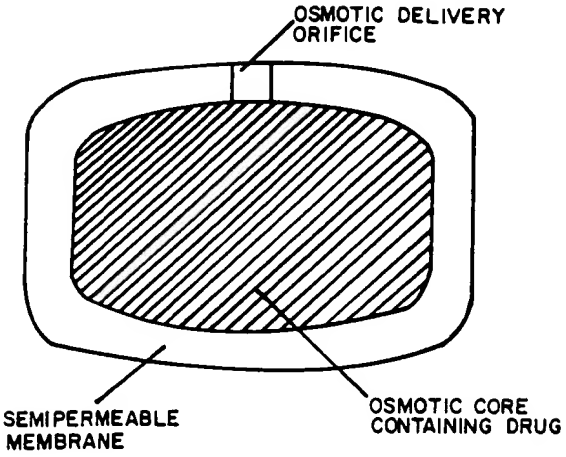


Figure 16 Elementary osmotic pump cross section. (From Ref. 12, used with permission.)

tablet will delivery, in any time interval, a volume of saturated solution equal to the volume of solvent uptake. The delivery rate is constant as long as an excess of solid is present inside the device, declining parabolically toward zero once the concentration falls below saturation, as is shown in Figure 17.

The principles upon which this device is based were presented earlier in this chapter. A key factor in proper drug delivery is the size of the

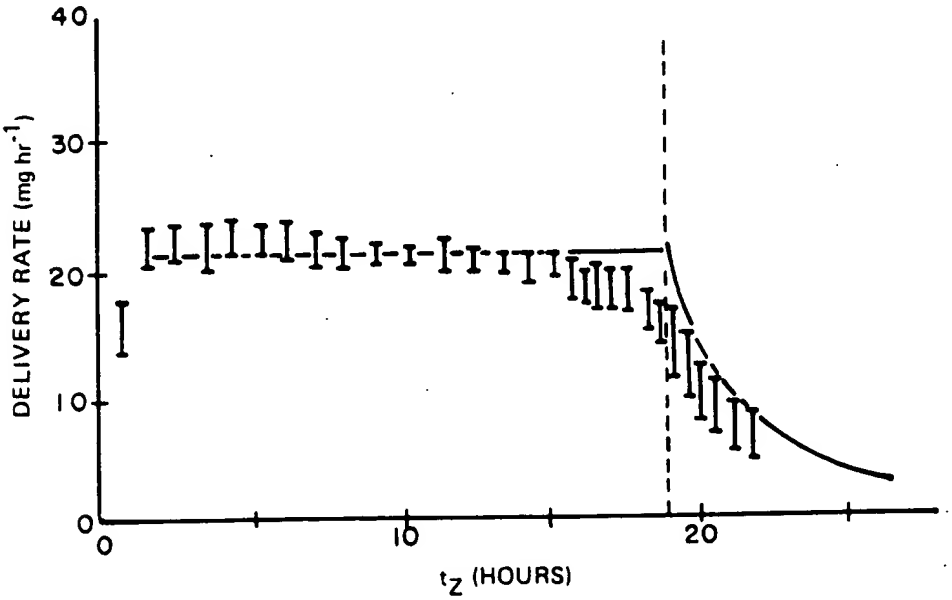


Figure 17 In vitro release rate of potassium chloride from elementary osmotic pump in water at 37°C. (I) range of experimental data obtained from five systems, (———) calculated release rate. (From Ref. 12, used with permission.)

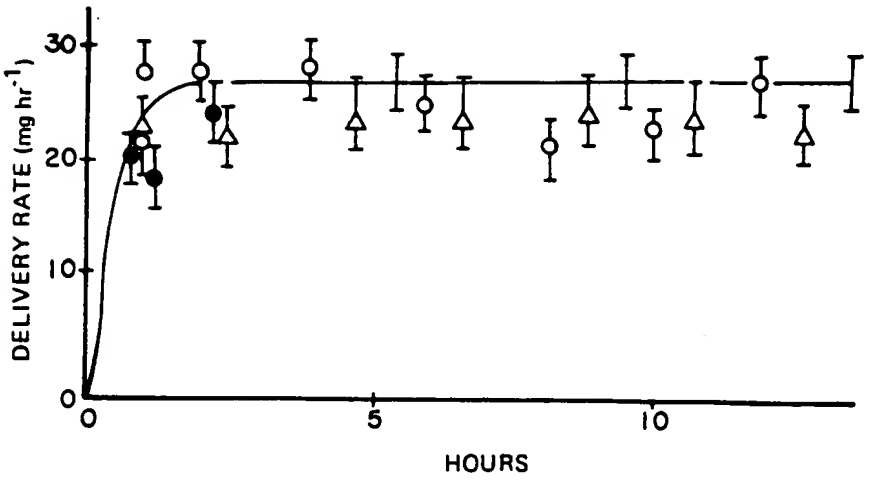


Figure 18 In vitro and in vivo release rate of potassium chloride from elementary osmotic pumps. (———) average in vitro rate from systems of the same batch; and (△), (○), (●) average release rate in one system in the GI tract of dogs 1, 2, and 3, plotted at the total time period each system resided in the dog. (From Ref. 12, used with permission.)

delivery orifice. Two conditions must be met, relative to the size of the delivery orifice, in order for it to be successful.

1. It must be smaller than a maximum size, A_{max}, to minimize the contribution to the delivery rate made by solute diffusion through the orifice.
2. It must be sufficiently large, above a minimum size, A_{min}, to minimize hydrostatic pressure inside the system that would affect the zero-order release rate.

Too small a hole will depress the delivery rate below that of the desired constant delivery.

In vivo tests in three dogs are shown in Figure 18. That zero-order release is maintained for long periods is evident.

It should be quite obvious from the mechanistic description of this apparatus that drug delivery would be independent of stirring rate and independent of pH. These are sizable advantages to a sustained release system and have indeed been shown operable both in vitro and in vivo.

V. COATING MATERIALS

Other sections of this text have dealt with coating substances insofar as describing their properties, coating technology, quality control, etc. Some of these coating materials, for conventional coating purposes, can be employed to produce sustained-release products dep nding on the thickness of coat employed as well as addition of fillers t the coating substance. Table 20 lists some of the more common coating substances and their properties. This listing is not intended to be compreh nsive, but

Table 20 Coating Materials and Their Properties

Type of coating	Most suitable dosage form(s)	Examples	Probable release mechanisms	Properties
Barrier coating (includes micro-encapsulation)	1. Film-coated tablets 2. Film-coated pellets or granules placed in gelatin capsules 3. Compressed tablets containing mixtures of barrier-coated particles with filler particles 4. Compressed tablets containing only barrier-coated particles forming a matrix	Various shellacs [18] Beeswax [18] Glyceryl monostearate [18] Nylon [18] Acrylic resins [18] Cellulose acetate butyrate [20] dl-Polylactic acid [20] 1,6-Hexanediamine [20] Diethylenetriamine [20] Polyvinylchloride [20] Sodium carboxymethylcellulose [243] Various starches [244] Polyvinylpyrrolidone [245] Acetylated monoglycerides [245] Gelatin coacervates [211] Styrene/maleic acid copolymer [245]	1. Diffusion and dialysis 2. Some disintegration possible 3. Also have had pH-dependent dissolution and some enzymatic breakdown incorporated into some films, but these are, therefore, poor "barriers"	1. Slow or incomplete release 2. Coating is subject to fracture during compression 3. Release depends on solubility of the drug and pore structure of the membrane 4. Obtain constant release when water or GI fluids pass through barrier to dissolve drug and form a saturated solution within the tablet

Table 20 (Continued)

Type of coating	Most suitable dosage form(s)	Examples	Probable release mechanisms	Properties
Barrier coating (includes microencapsulation) (cont)		Gelatin coacervates [88] Styrene/maleic acid copolymer [124]		
Embedment into a fatty coating (similar to embedding in a matrix of fatty materials)	1. Compressed granules into a tablet 2. Compressed granules placed in a gelatin capsule 3. Multilayered tablets 4. Compression-coated tablets	Glycerol palmitostearate [18] Beeswax [18] Glycowax [18] Castor wax [18] Carnauba wax [18] Glyceryl monostearate [18] Stearyl alcohol [18]	1. Gradual erosion of the coat, aided by pH and enzymatic hydrolysis of the fatty acid esters 2. Coating may contain portion of the dose for quick release upon hydrolysis with subsequent slow release from erosion of core	1. Slow or incomplete release 2. Difficult to control release pattern due to variations in pH and enzyme content of the GI tract
Repeat action coatings	1. Sugar coating of an enteric-coated core tablet 2. Compression coating of an enteric-coated core tablet	Cellulose acetate phthalate [18] (Many of the examples listed for "Barrier Coating" apply here also)	1. pH-Dependent dissolution and enzymatic breakdown 2. Outer coating releases first dose rapidly in stomach fluids, inner enteric-coated core releases a second dose at	1. Variations due to changing stomach emptying times 2. Not a "true" sustained form as defined in text

			some later time in intestinal fluids	
Coated plastic matrix	1. Multilayer tablets 2. Compression-coated tablets	Polyethylene [18] Polyvinylacetate [18] Polymethacrylate [18] Polyvinylchloride [18] Ethylcellulose [18] Silicone devices [20] Methylmethacrylate [20] Ethylacrylate [20] 2-Hydroxyethylmethacrylate [20] 1,3-Butyleneglycoldimethacrylate [20] Ethyleneglycoldimethacrylate [20]	1. Outer coating containing active drug dissolves rapidly to provide drug for immediate absorption 2. Above process is followed by leaching of drug from inert matrix via penetration of GI fluids into pores of the matrix	1. Slow or incomplete release 2. Only water-soluble or fairly water-soluble drugs can be used 3. Plastic matrix skeleton is excreted in its original shape in the feces 4. Drug liberation depends only on solubility in GI fluids, completely independent of pH, enzyme activity, concentration, or GI motility
Coated hydrophilic matrix	1. Multilayer tablets 2. Compression-coated tablets	Carboxymethylcellulose [18] Sodium carboxymethylcellulose [18] Hydroxypropylmethylcellulose [18] Methacrylate hydrogels [19] Polyethyleneglycols [106]	1. Outer coating containing active drug dissolves rapidly along with rapid dissolution from the surface of the matrix to provide drug for immediate absorption	1. Drug liberation rate is dependent on type and amount of gum used 2. High water solubility of the drug is absolutely necessary

Table 20 (Continued)

Type of coating	Most suitable dosage form(s)	Examples	Probable release mechanisms	Properties
Coated hydrophilic matrix (cont)			2. Above process continues until a viscous gelatinous barrier is formed around the matrix surface 3. Once the gelatinous barrier has formed, diffusion and dissolution, via erosion, occur at a slow, controlled rate	3. Release is controlled by drug diffusivity more than by gum dissolution or water penetrability as long as the hydrated gelatinous layer r - mains intact

rather is a starting point for the formulator interested in preparing a sustained-release product through coating.

VI. SUMMARY

During the past several years we have witnessed an increased number of publications dealing with polymer coatings as a means of sustained drug action. Most of these approaches have been aimed at the parenteral or specialty areas and as yet many have not been brought to the market stage, but their potential utility is apparent. Our ability to manipulate film properties gives us a powerful tool by which to prolong drug delivery and produce variable drug release rates. It seems reasonable to conclude that we are limited in attempting to produce variable release rates from conventional tablets or pellets if we rely strictly on dissolution rates and shape factors, but the addition of polymer coatings with variable properties gives us considerable latitude in producing sustained-release products with varying release rates.

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